PSJ3
Exhibit 193

DRAFT

Global Pain Strategy

GDC comment: Please note that comments from Gail Cawkwell on this slide deck are in yellow boxes

Alix's comments are in this color

6th June 2016

DRAFT

In 2016 we will develop a comprehensive short- and long-term strategic plan, with periodic working group meetings throughout the year

Overall objective: to collaborate in developing the key elements of our Global Pain Strategy and articulating these into a clear strategic rationale, including messaging for presentation to the Board

- We have performed baseline business and market analysis, culminating in a three day workshop designed to distil global stakeholder thinking on key market trends, business challenges and opportunities
- Our current work represents a further exploration of market and business opportunities arising from key trends, culminating with this presentation: a first working draft of the overall global strategy

2 March: GPWSG London meeting

15 April: working draft due to US leadership

26 April: working draft due to European leadership

26 May: final draft due to regional heads

6 June: Board presentation

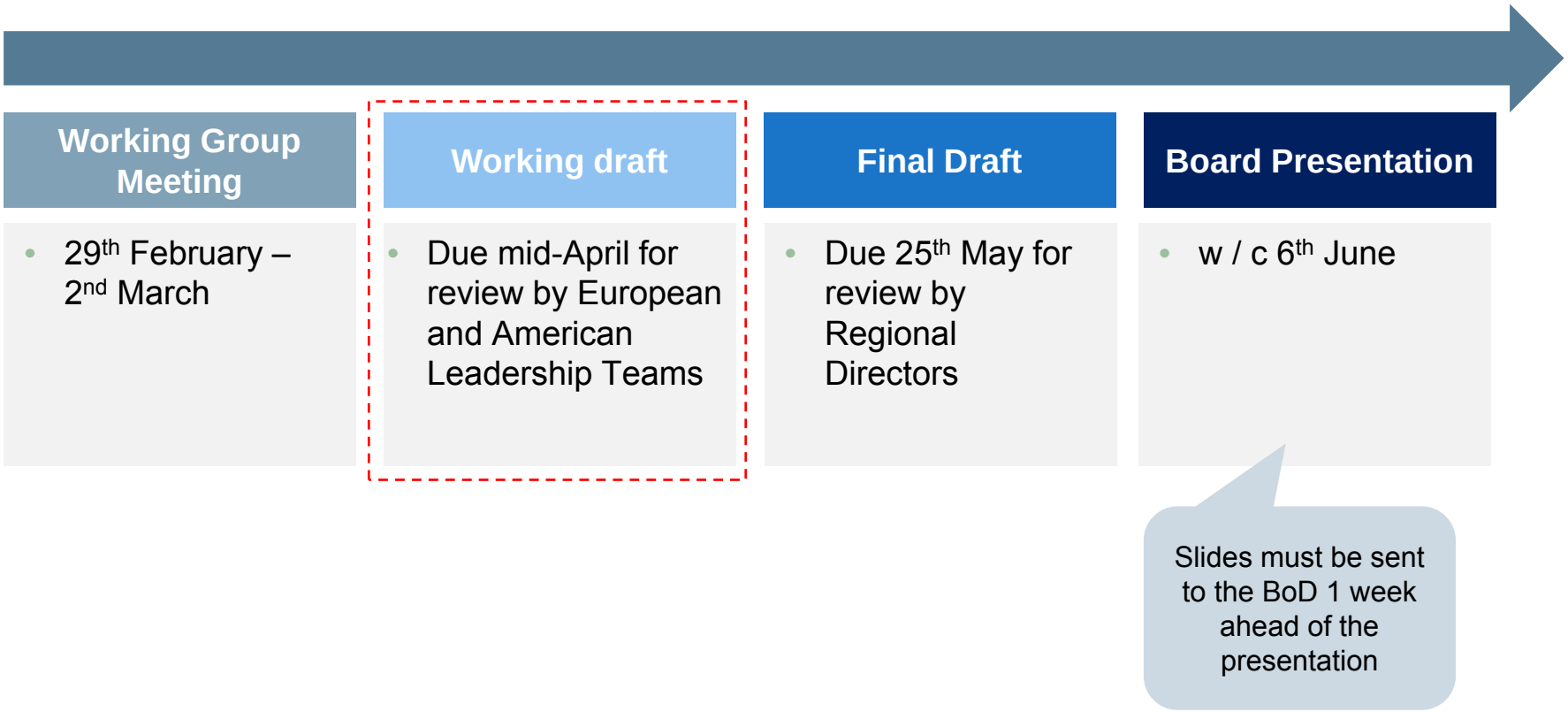
27 June: GPSWG Warsaw meeting (in person)

Post board meeting: Implementation & refinement

December: GPSWG meeting (in person)

DRAFT

As part of our yearlong strategic planning process, we will present the recommendations of the Global Pain Strategy to the Board in June



DRAFT

The Global Pain Strategy Working Group was convened to develop a comprehensive proposal to build a sustainable & growing pain franchise

Project sponsors: Mark Timney, Antony Mattessich

Project Leads: Kate Hurtig, D

David

What is JJ's full name? Katie's?

Anyone I am missing?

	US	Europe	MAL	Canada
Commercial	**David Xu** **Saeed Motahari**	**Kate Hurtig**	**Telea Herpin**	**Graham Watson**
R&D	**Alan Dunton** **Don Kyle**	**Karen Reimer** **Petra Leyendecker** **Alexander Oksche**		**Julie Ducharme**
Medical Affairs	**Gail Cawkwell** **Alix MacLean**	**Harry Smith**	**Dora You**	
Business Development	**Ann Kraft**	**Allen Downs**		

Supporting: Maya Marescotti, Katie XXXX, Shacker Mourad, Chloe Maya, Peter McGowan, JJ XXX

Executive Summary

- **Pain remains an attractive market:**
  - The pain market is large and fragmented with significant unmet needs
  - The unmet needs drive the continued search for novel targets to manage pain
  - Our core capabilities in opioids and chronic pain are the ideal springboard to expand into broader pain
- **Our vision: we can win in pain**
  - We aim to be a global leader in pain, with the unique capabilities & diverse portfolio to establish & sustain a market leadership position
- **Critical to achieving our vision are four strategic imperatives - we m**

Alix: Perhaps there's a better word/words than optimize as its not clear what that means ---- does it mean increase market penetration globally?

1. Optimize our current assets
2. Innovate in pain to lead scientific understanding to identify new targets, measures and treatments
3. Build a truly diverse portfolio that is driven by customer insights and patient need
4. Develop the right operational model

Our pain strategy is ambitious. We must drive a fundamental change in culture throughout the organisation and move from:

product thinking → portfolio thinking; Alix: remove ;

strong opioid/chronic pain expertise → multiple MoA/broad pain expertise and local working → global working

Agenda

1. **The pain therapy landscape**
2. **Our vision**
3. **Our strategic plan**

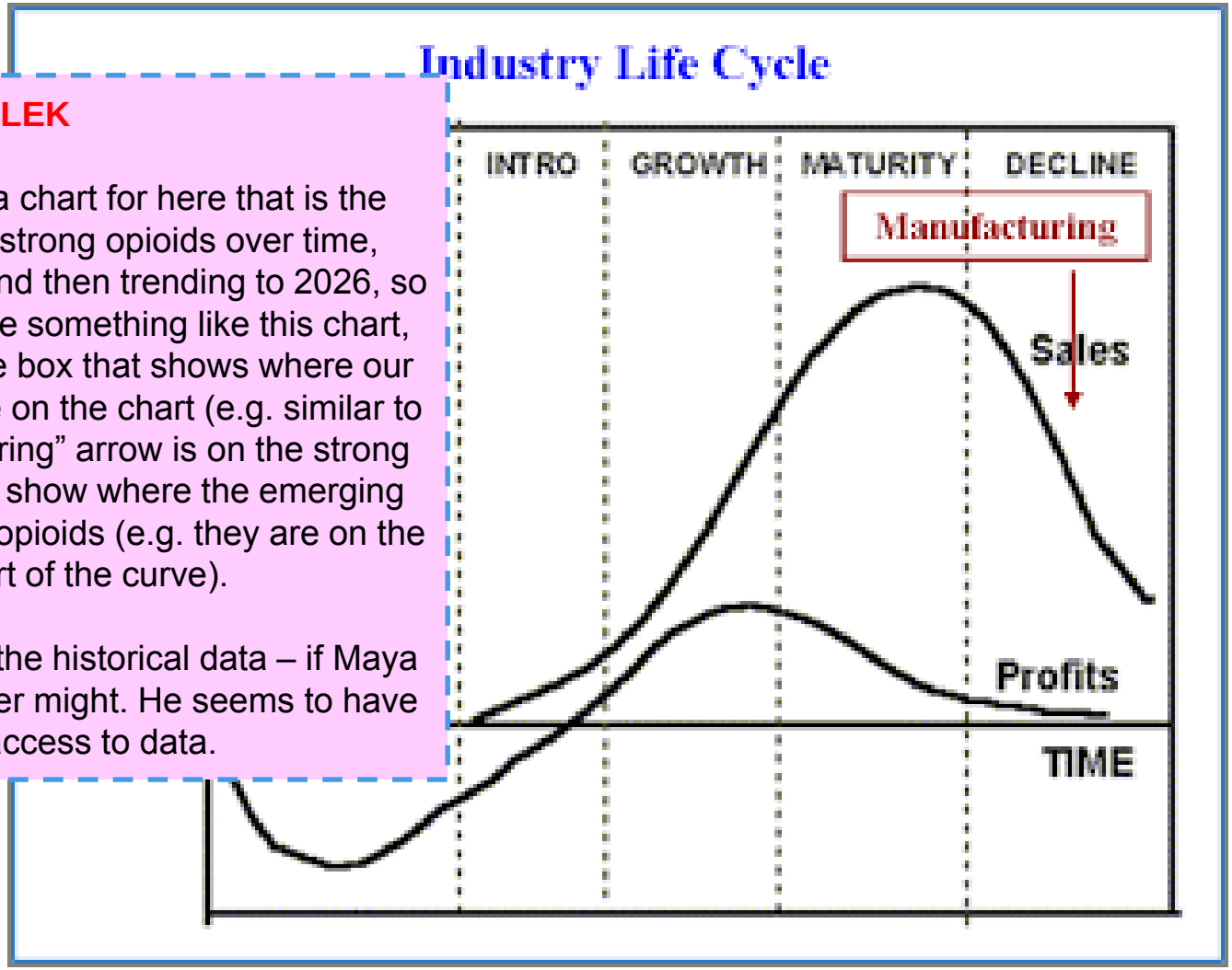
DRAFT

We are experts in strong opioids for the treatment of chronic pain, but while these medicines will remain important when used responsibly, the drive to limit their use will continue, particularly in the developed world

LEK

What I would like is a chart for here that is the global sales line for strong opioids over time, starting in the 1980s, and then trending to 2026, so that it will look in shape something like this chart, then I would like a little box that shows where our developed markets are on the chart (e.g. similar to where the "manufacturing" arrow is on the strong opioids line) and then show where the emerging markets are for strong opioids (e.g. they are on the growth part of the curve).

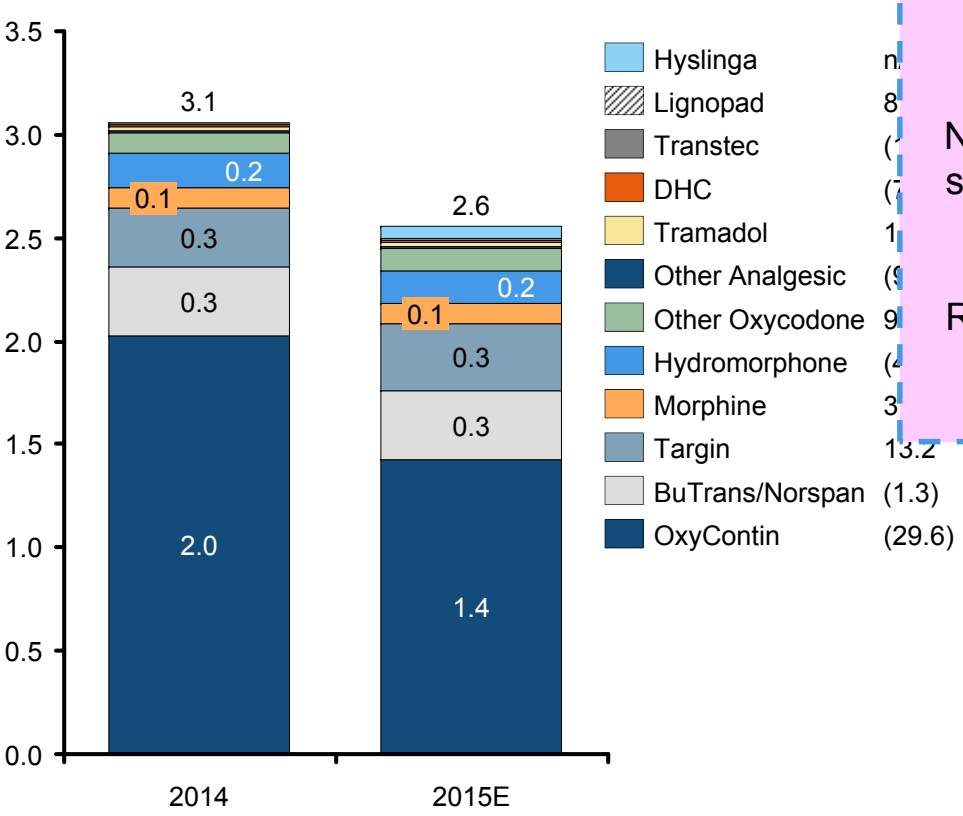
Not sure where to get the historical data – if Maya doesn't have it, Shacker might. He seems to have magical access to data.



2015 DATA

OxyContin has been one of the most successful medicines in the pharma industry, but it is now in decline, and our other pain products cannot compensate

Pain sales of our products by product (2014-15LE)
Billions of U.S. dollars

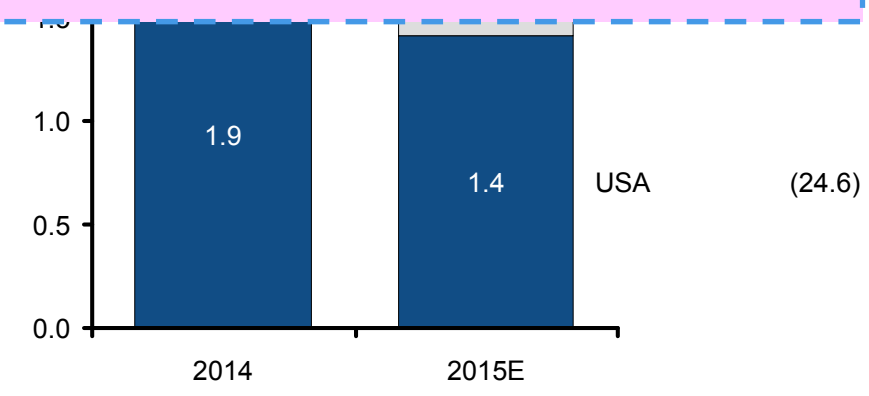


LEK

Can we get data about top selling pills of all time, cumulative sales? I bet OxyContin is at the top of that list….

Not just about sales, but about longevity? Can we find something, maybe I am wrong… it just seems to keep going and going and going and going

Remove split by region on the right side and just have the sales over time



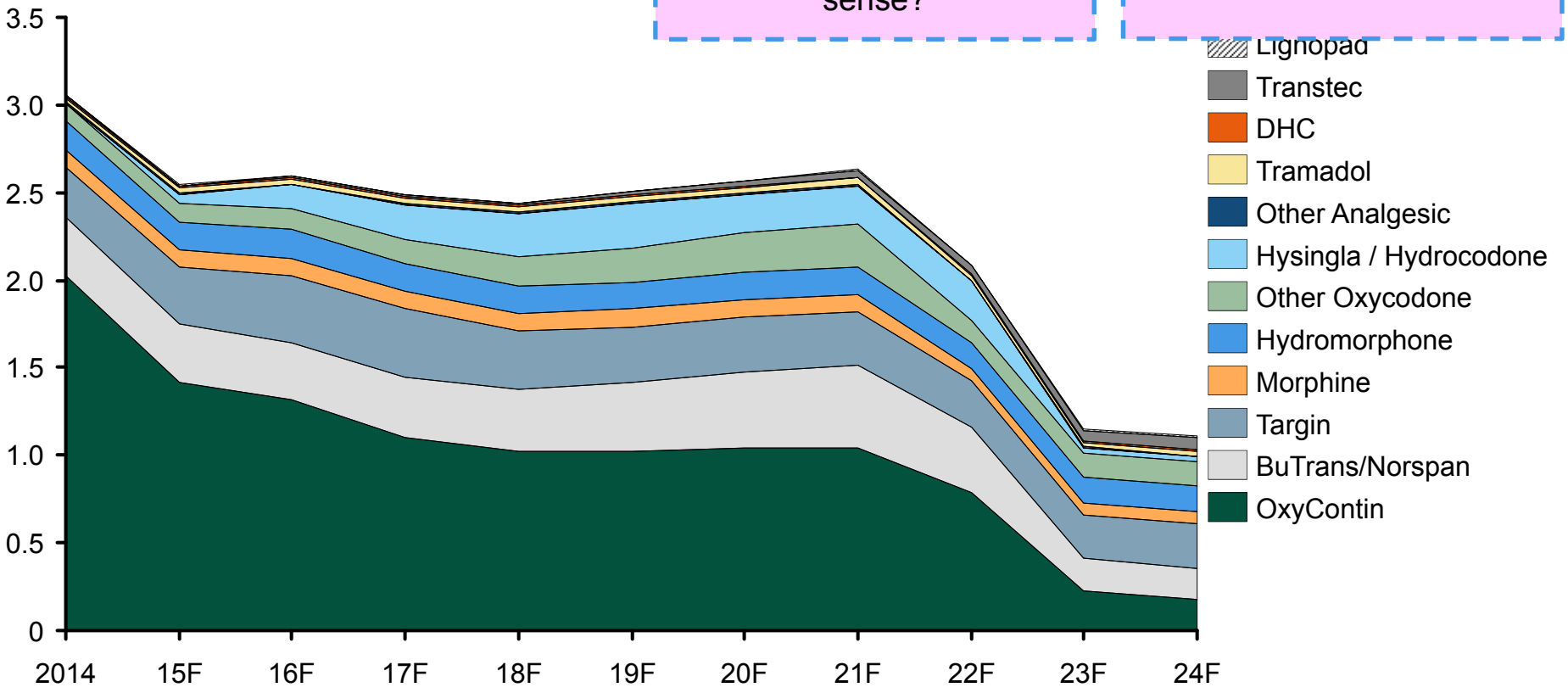
2015 DATA

Our in-line portfolio will provide mid-term cash flow but will decline materially by 2025, due to the concentrated nature of our portfolio

LEK
Should we merge the slide before with this slide? Maybe that makes more sense?

Chloe
Do we have 10 year plan updated financials yet so we can pull out the pain extract?

Global pain portfolio net sales – June 2015 (2014-24F)
Billions of dollars



Note: * Forecasts for EU region from 2015F to 2021F are from Nov 2014

DRAFT

Going forward, we must diversify away from opioids and chronic pain in order to de-risk and leverage our position to capture opportunities in pain

Opioids, on their own, are not the most attractive pain segment for us

- The opioid market is in decline, due to:
  - increased restrictions on prescribing
  - competitive intensity in ADFs and genericisation
  - EU customers' reluctance to use opioids in chronic pain; global customers looking beyond opioids for pain relief
  - restrictions and difficulties with reimbursement of opioids in emerging markets
- Opioids make up only 13% of the prescription pain volume market: we are not playing in the majority of the market

Significant unmet needs remain in pain

- Despite the availability of treatments, customers and patients are dissatisfied with:
  - efficacy, particularly in neuropathic pain conditions
  - safety and tolerability
- These unmet needs are driving scientific research to novel targets and mechanisms

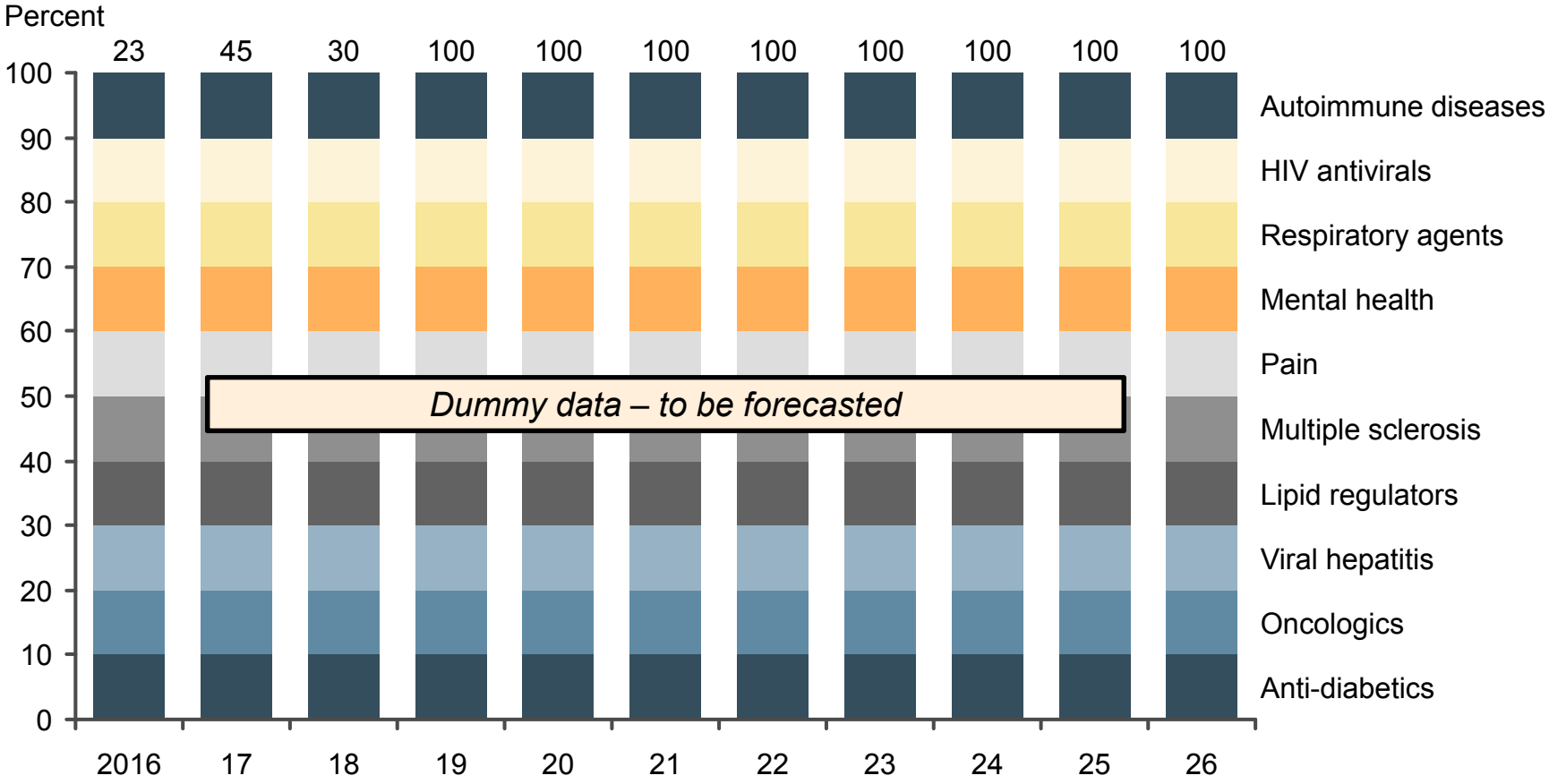
We are in a strong position to broaden our reach in pain beyond opioids

- We have a high level of understanding of pain, customers and patients due to our history in opioids
- We are already on the journey to diversification through pipeline products Sigma and TRKA
- More can be done; we must continue to build a broad pain pipeline

DRAFT

The overall pain market is large and will continue to be the largest Rx pharmaceutical market by volume

Proportion of global pharmaceutical volume by therapeutic area (2016-26)

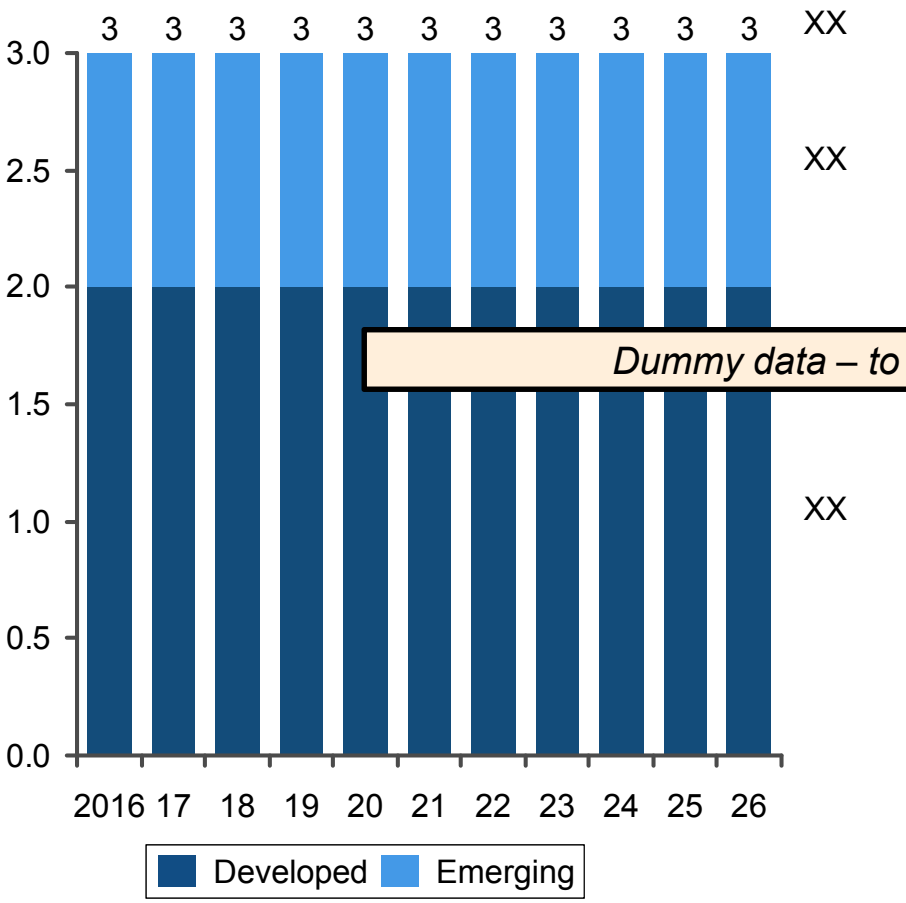


Note: CAGR % is for 2010-2014
Source: IMS MIDAS MAT Q4 2014; IMS MEDICAL MAT Q4 2014

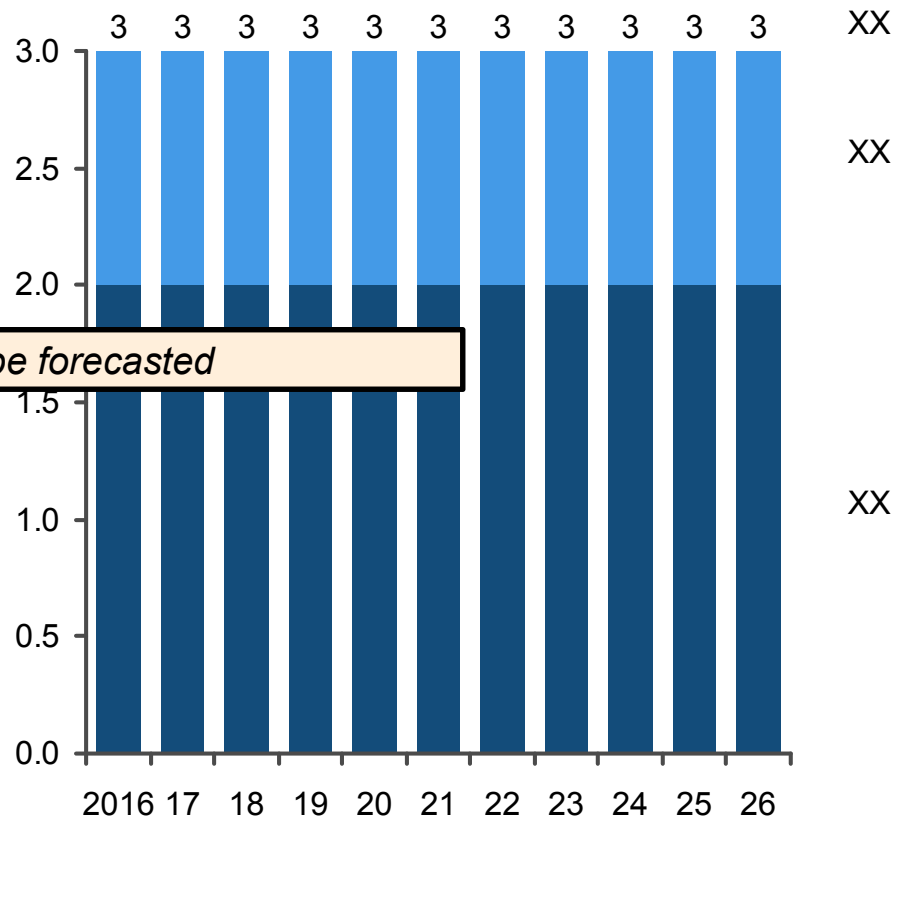
DRAFT

Developed markets will continue to represent the larger share of both the value and volume of sales in the pain market in the future

Global pain market value (2016-26)
Billions of USD ($)



Global pain market volume (2016-26)
Billions of standard units (STU)



Dummy data – to be forecasted

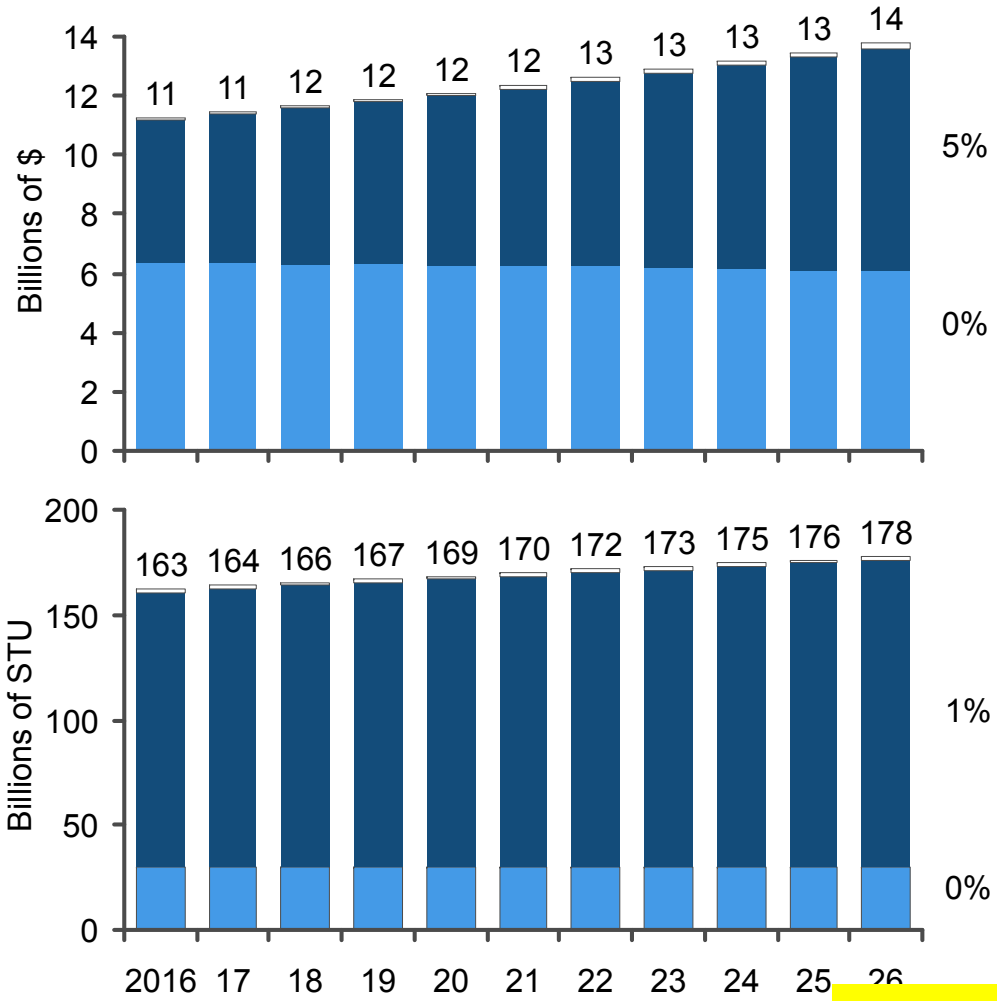
Note: Geographies include - Developed: EU5, USA, Australia, Canada, Japan, Emerging: Brazil, Russia, India, China, Mexico, Indonesia, Egypt, Turkey, Saudi Arabia (ROW, scaled up to 1.25)
Source: IMS MIDAS sales MAT Dec 2015

DRAFT

Most of the current top pain brands will lose exclusivity by 2022, so all new entries will have to demonstrate significant value to patients and payers over the generic SoC

INDICATIVE

Global pain market size (2016-26)*



Note: Geographies include EU5, USA, Australia, Canada, Japan, Brazil, Ru
based on 2010-15 growth rate, continued through 2026

Source: IMS MIDAS sales MAT Dec 2015

Launch and LOE for top brands by value and volume

Branded drug	Launch year	LOE year
LYRICA PREGABALIN C		2018
OxyContin		
SUBSYS (fentanyl sublingual spray) 100,200,400,600,800,1200,1600 mcg	*To be filled in*	
RELPAX (eletriptan HBr) 40 mg		
NORSPAN buprenorphine transdermal system		
NUCYNTA TAPENTADOL		
opana ER (oxymorphone HCl) EXTENDED-RELEASE TABLETS		
TARGIN		2017
Duragesic		
Campath Alemtuzumab For Intravenous Use Only illuminating possibilities		

Generics Non-generics Other

Work-in-Progress

DRAFT

Overall in pain, neuropathic pain is the fastest growing segment, although chronic musculoskeletal pain, an area where we play, makes up the largest segment by both value & volume

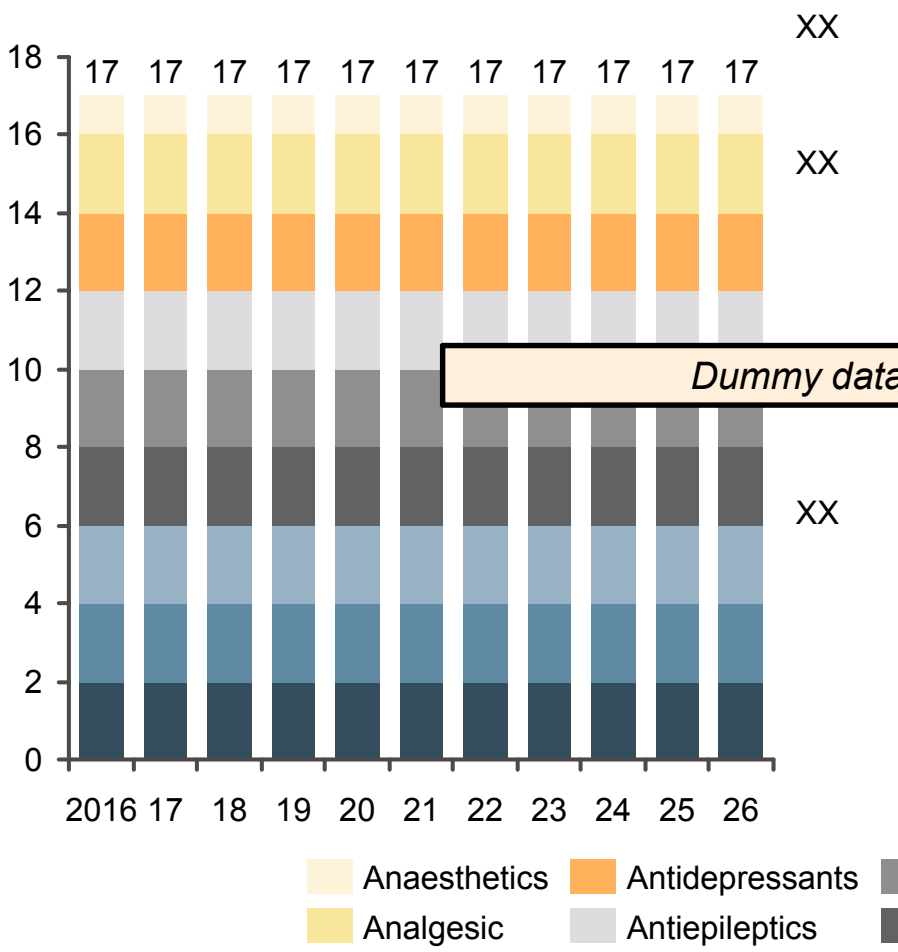
LEK

Would you please get from Maya the estimated value of the indications within pain - and the split of the global value of the different sub-indications:

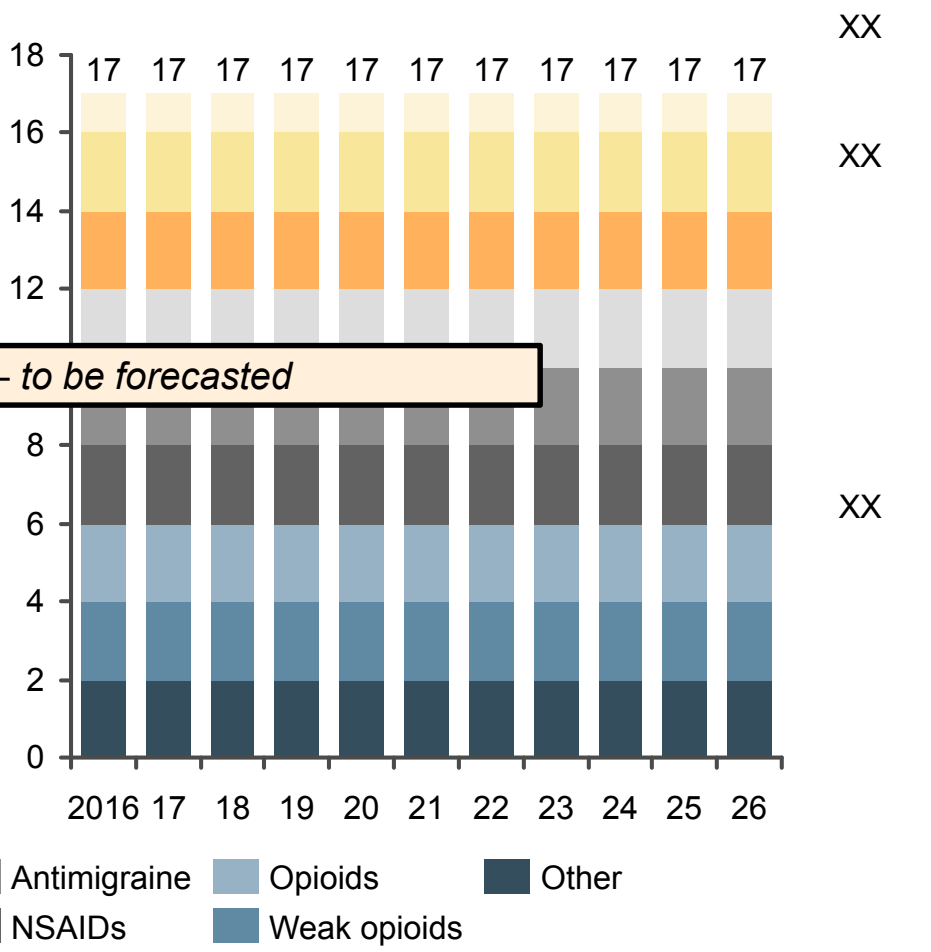
DRAFT

However, our focus market of strong opioids makes up only 13% of the volume of the market, declining due to increasing restrictions on prescribing and HCPs' preference to limit use of stronger opioids

Global pain market value (2016-26)
Billions of USD ($)



Global pain market volume (2016-26)
Billions of standard units (STU)



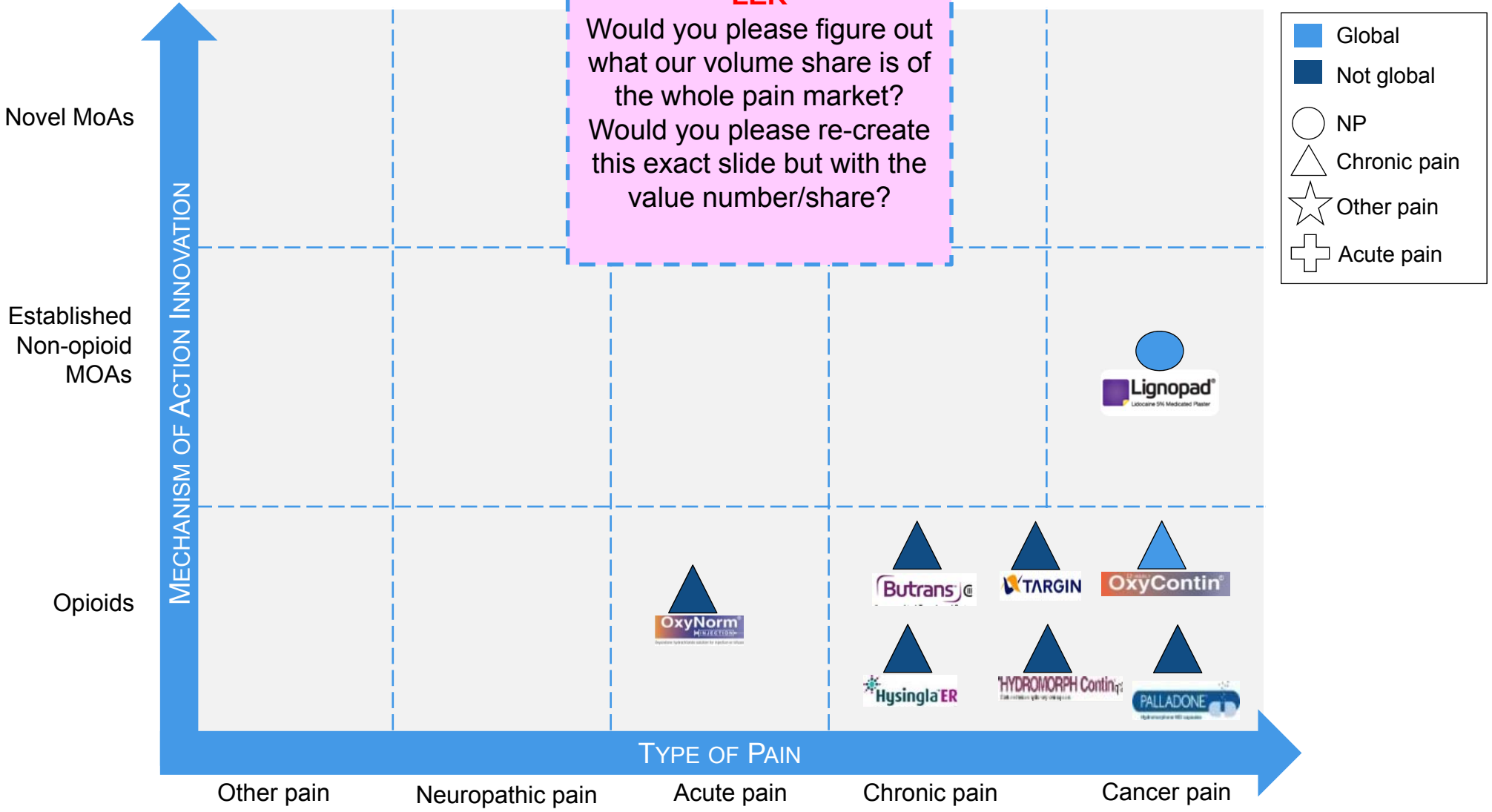
Anaesthetics
Analgesic
Antidepressants
Antiepileptics
Antimigraine
NSAIDs
Opioids
Weak opioids
Other

Source: IMS MIDAS MAT Q4 2015, IMS MEDICAL MAT Q4 2015

DRAFT

Mundi/Purdue's share is X% of the volume of the overall pain market – our current business is highly concentrated & the problem of pain is not yet solved

LEK
Would you please figure out what our volume share is of the whole pain market? Would you please re-create this exact slide but with the value number/share?



Source: Mundipharma & Purdue

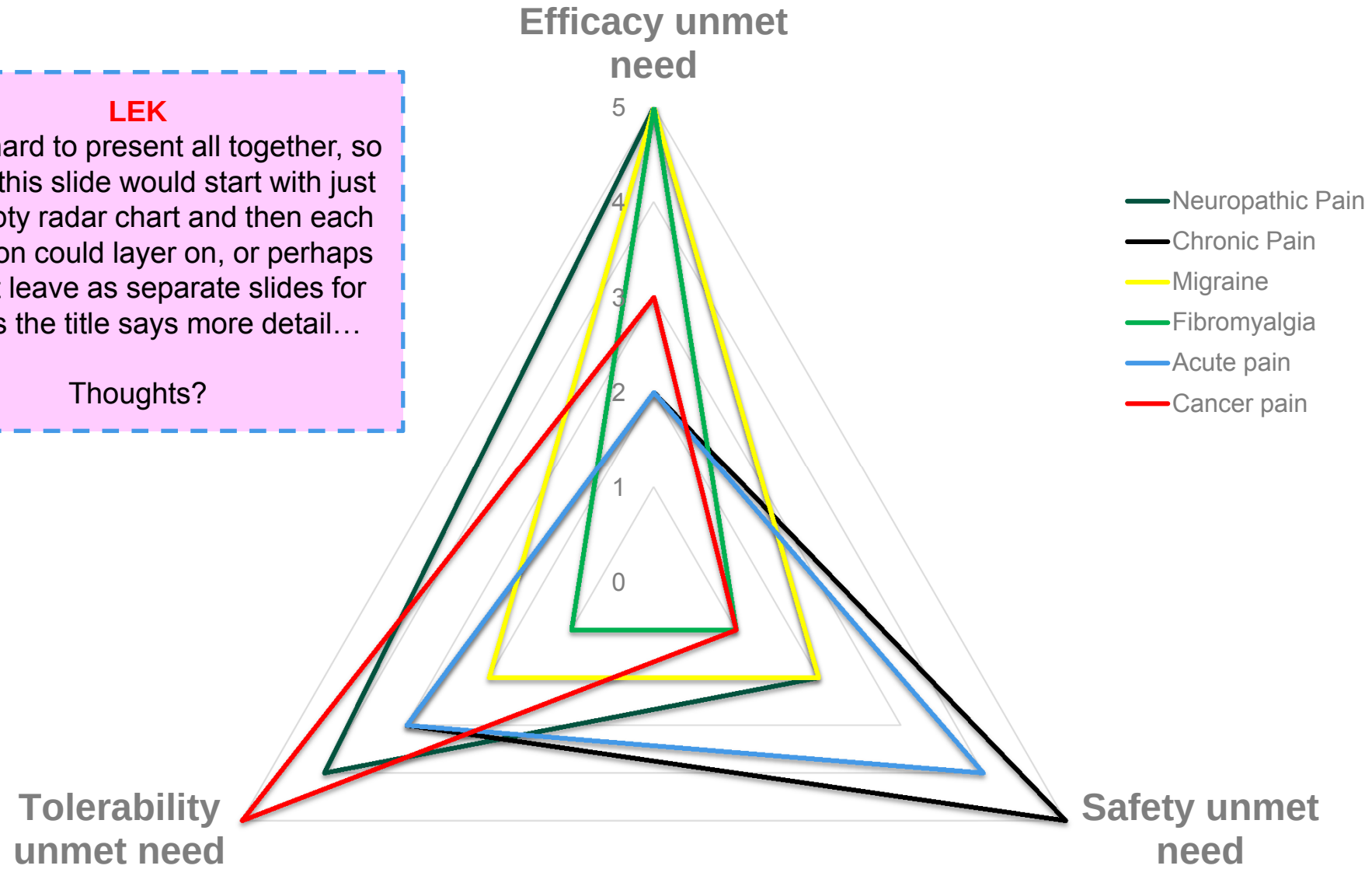
DRAFT

Customer insights have reinforced to us that even though many treatments exist for pain, unmet needs remain, though the nature of the need varies by indication

LEK

This is hard to present all together, so ideally, this slide would start with just the empty radar chart and then each indication could layer on, or perhaps we just leave as separate slides for now as the title says more detail…

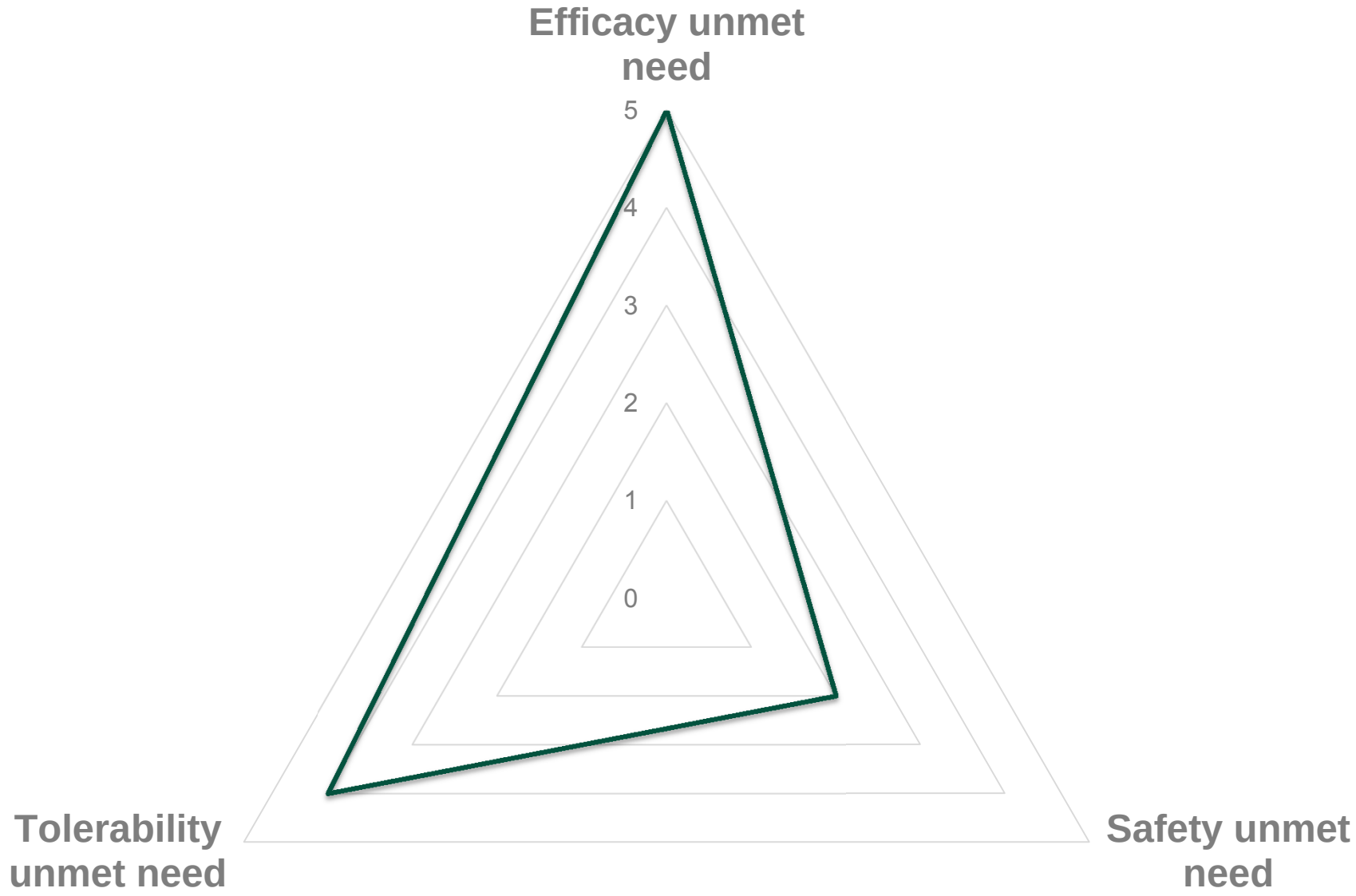
Thoughts?



5 – High; 1 - Low

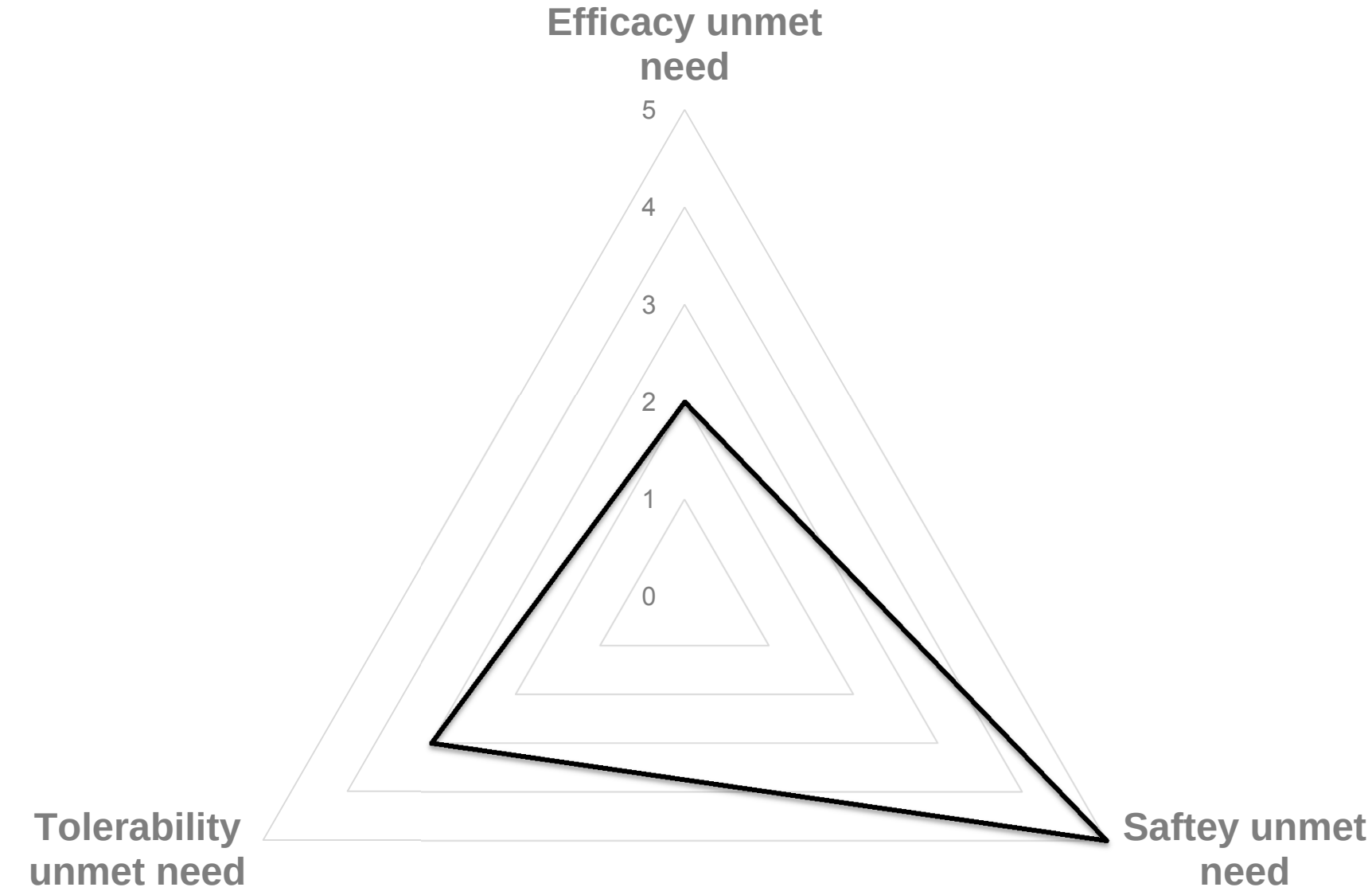
DRAFT

Unmet needs in neuropathic pain: the ideal TPP would be for a product that could reliably reduce pain, both depth & breadth of patients, without sending them to sleep, giving them headaches, weight gain or skin irritations



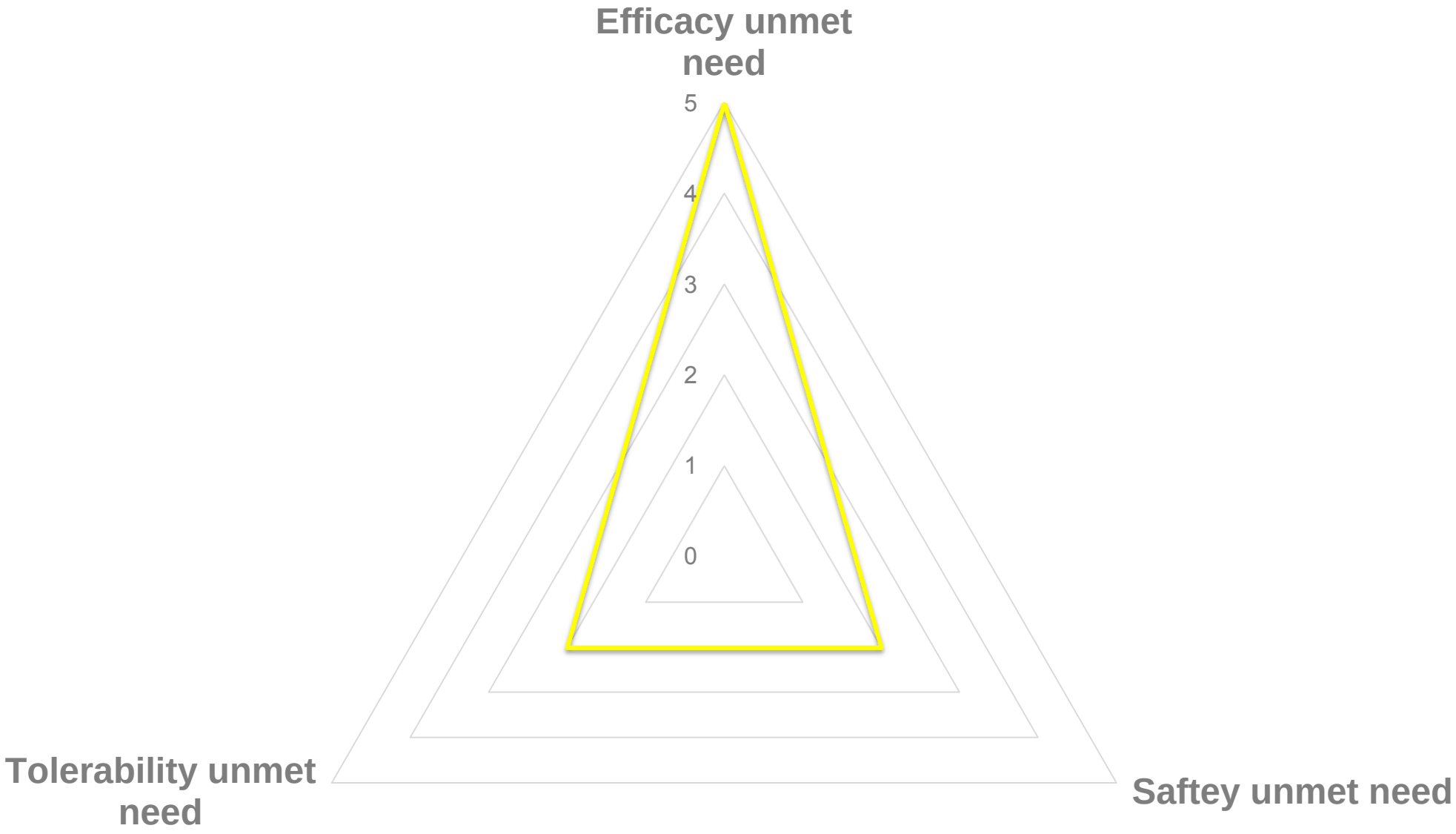
5 – High; 1 - Low

Unmet needs in chronic pain– the ideal TPP would be for a product that could deliver strong opioid-like efficacy, without the risk of tolerance, euphoria, addiction and respiratory depression; tolerability improvements would be nice to have



5 – High; 1 - Low

Unmet needs in migraine – the ideal TPP would be for a product that could reduce the frequency and severity of migraine attacks as well as prevent attacks from happening in the first place



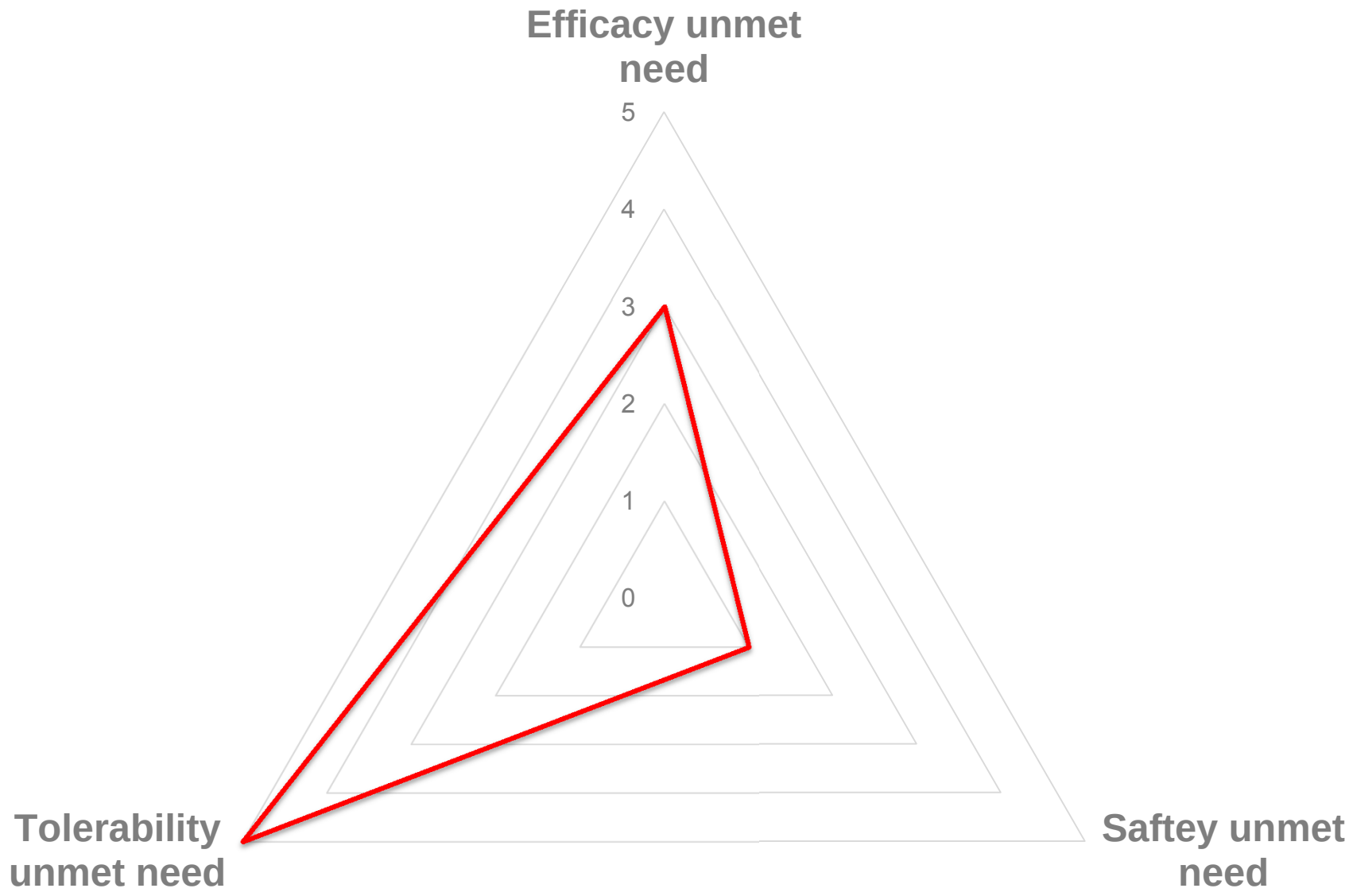
5 – High; 1 - Low

DRAFT

Unmet needs in fibromyalgia– the ideal TPP would be for a product that would reduce pain in a more homogeneous sub-population that could be identified using a bio-marker

5 – High; 1 - Low

Unmet needs in Cancer pain– the ideal TPP would be for a product that would give the same efficacy as high dose strong opioids, without the somnolence, euphoria and other side effects related with opioids, such that the patient can have some QOL during their remaining time

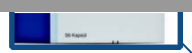


5 – High; 1 - Low

DRAFT

Pain is a complex CNS condition with multiple potential targets, success in developing new treatments

Successful innovation



pregabalin 2004

Strong Opioids

ADF strong opioids

Failed innovation

Calcium Channel Inhibitors

TRPV-1 antagonists

Biomarkers for fibromyalgia

Cannabinoid receptor agonists

Objective measures of pain

Pre 20th century → 1950s → 1970s → 1990s → 2000s

DRAFT

While innovation in pain has met with limited success, recent advances mean that now is the time to get in front of the curve and take leadership in the advancement of science

Alix: regenerative medicine is coming

Thomas Klein

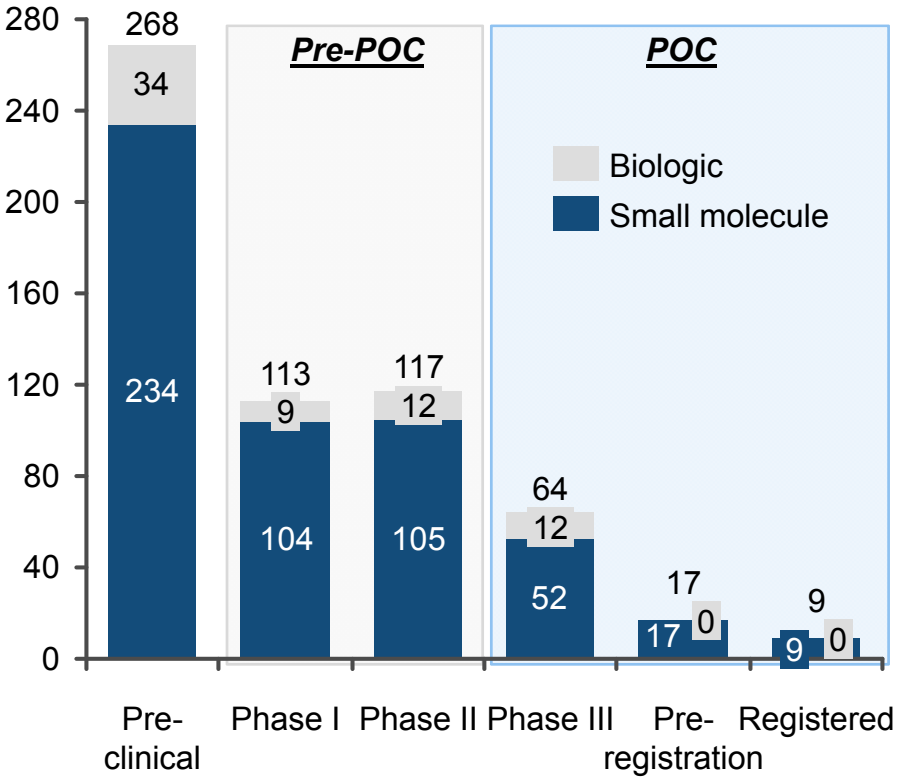
Thomas – would you be able to list out what is going on now, and what has happened in the science of pain over the last 5 years? What has changed? What are the new things that we now know? Because some MoAs failed, did we learn anything further? When did the knock out mice with congenital insensitivity to pain happen & what did we learn? Is there something with new genetic mapping technologies that can help? Are there are new biomarker ideas that we can do/use? What new discoveries are on the cusp of happening? Et~

DRAFT

This has led to a large industry pipeline, with approx. 590 assets in development for pain and only 20% of the pipeline remaining focused on opioids

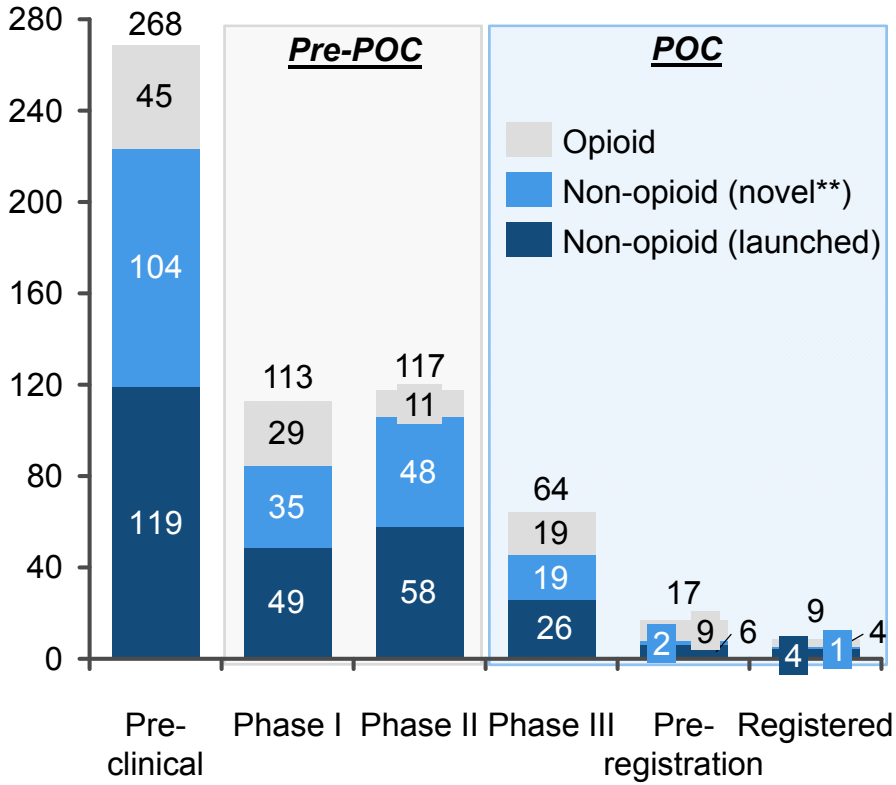
Number of unique assets in development for pain* (February 2016)

Number of assets



Number of unique opioid and non-opioid assets in development for pain* (February 2016)

Number of assets



The pain pipeline is generally larger than other therapeutic areas, e.g. diabetes (~525 assets in development), cardiovascular^ (~525), hypertension (~250), and asthma (~230)

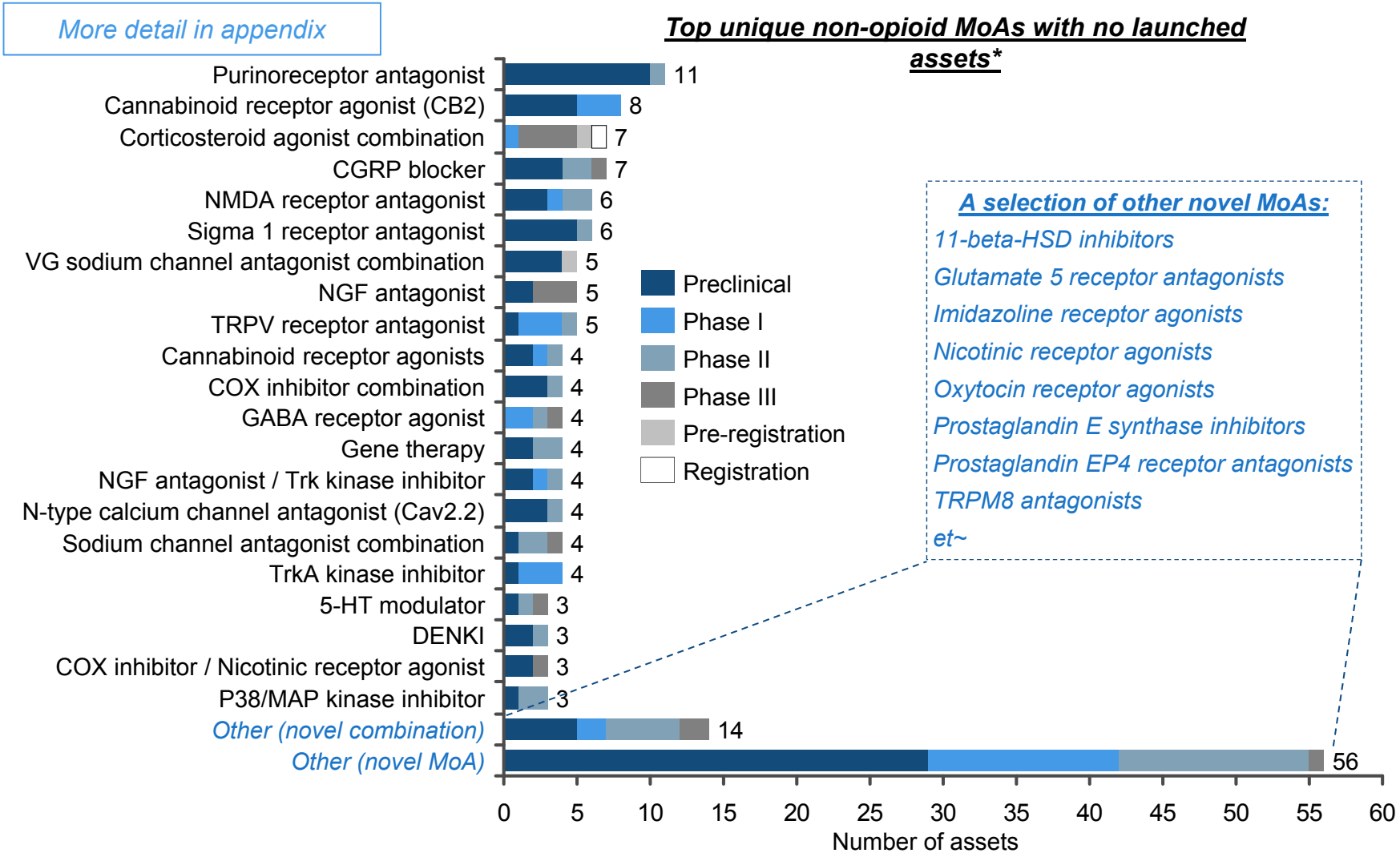
Note: * Includes pain-related indications, such as opioid-induced side effects and anaesthesia adjuncts. ** Assets have been defined as "novel" if no pain products have been launched with the same MoA. Assets in development by Mundipharma/Purdue or related entities are included in this analysis; ^Cardiovascular excludes hypertension

Source: PharmaProjects

To incorporate Alan Dunton's work and split into Ph3 vs. earlier assets

Pain is not yet solved, and unmet needs remain – this drives the search for greater understanding of the mechanisms of pain, and potential new targets for medicines

More detail in appendix



Abbreviations: 5-HT, 5-hydroxytryptamine receptor; VG, voltage-gated; NGF / TrkA, Nerve Growth Factor Tyrosine Kinase; CGRP, Calcitonin gene related peptide; DENKI, Dual enkephalinase inhibitors; MAP kinase, Mitogen-activated protein kinase; TRPV, transient receptor potential vanilloid.

Note: * Unique assets counted based on latest phase for a pain-related indication. Some assets are combinations of MoAs for which launched products exist, therefore list also includes assets that combine a novel MoA with an older MoA. Such combinations have been included within the segment of the novel MoA.

Source: PharmaProjects

DRAFT

Those doing the investing in pain are a relatively concentrated group... (revise with new info pre below)

Pfizer — 9% of global pain market

GRÜNENTHAL — 3% of global pain market

Lilly — 1% of global pain market

Lyrica (Pr
2014 sa

Celebrex
2014 sa

(Duloxetine)
les: $250M

Lidoderm
(Lidocaine
2014 sa
$160M

Voltaren g
(Diclofena

2014 sales: $180M

Opana ER

(paracetamol and oxycodone)

RDUE

pharma

LEK

We need a complete rework of this slide please.

I think David has already sent you details on the analytics we would like here, but just to reiterate, the idea is to have a look at who the branded players are, who is investing in R&D, who are the folks that have all the pre clinical and clinical work ongoing in pain (R&D spend may not show the preclinical/phase I work yet), and who have a strategic intent to be in pain, as well as who is partnering in pain.

And then show their share of global pain sales. Then show ours. Awesome.

Shacker had a table? Not sure if it was comprehensive…

Note: Global pain market share reflects the revenue from each company's branded pain products as a percentage of the global pain market sales provided by IMS
Source: IMS; company websites and press releases; EvaluatePharma; Pipeline

DRAFT

While we have historically focused on opioids and chronic pain, we have the right core capabilities and are in a unique position to become true leaders in pain

- Relationships with the top experts in pain globally
- Commercial reach/depth with the right prescribing customers
- IP
- Policy
- Supply chain
- Global strategic decision making, but local implementation
- Family owned so can have long term focus

David/Kate/Graham/Telea

To rework this with feedback from the 4 RDs on what exactly our core capabilities are and answer the question “why us”

Agenda

1 **The pain therapy landscape**

2 **Our vision**

3 **Our plan**

Our Vision

Our vision

We will be the global leader in pain, innovating to deliver meaningful clinical benefit to patients and HCPs

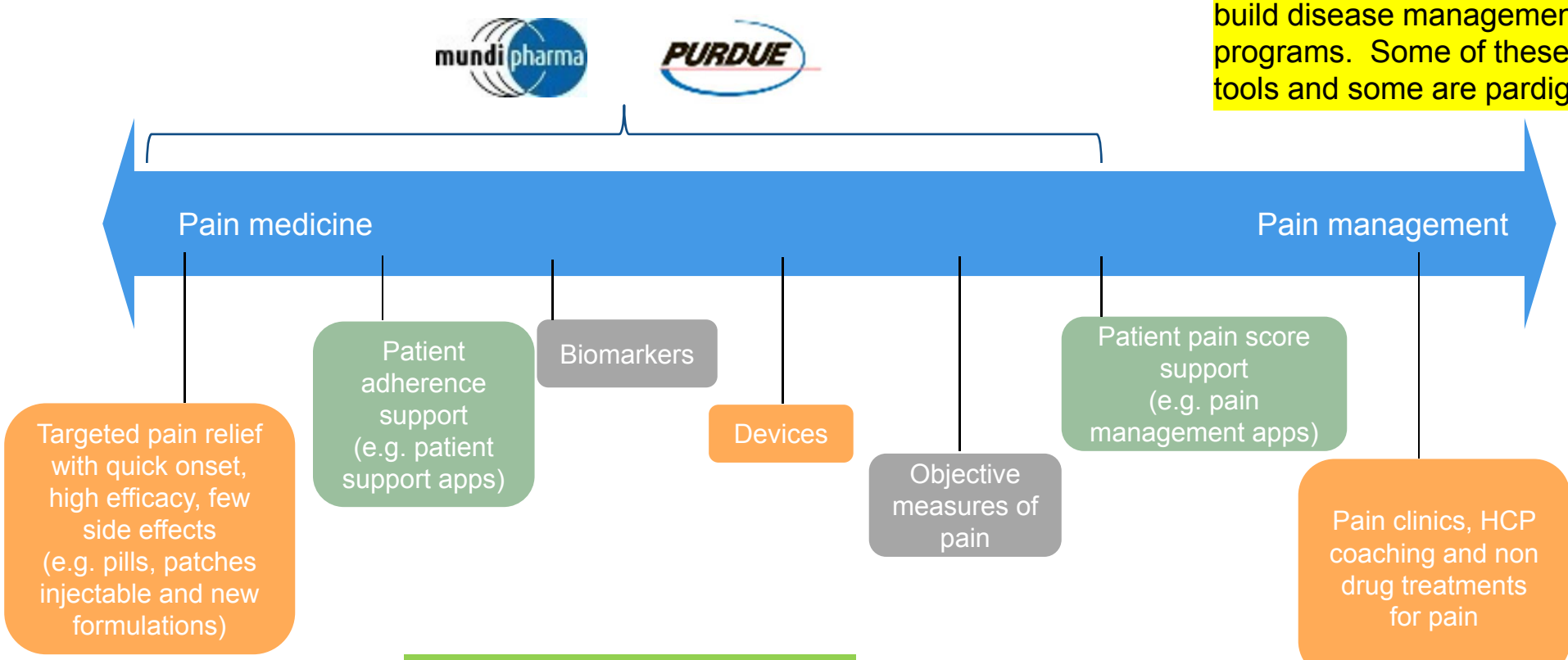
What leadership means

- Leadership to patients means we invest our time and energy to gain **deep insight** so that we truly **understand what is driving the unmet need**
- Have a ***diverse portfolio*** and a strong pipeline with a range of MoAs, indications, and development phases
- Develop a credible reputation as a ***scientific leader in pain***, with a ***virtual discovery engine***, attracting academic partners & regulatory collaboration
- Behave as a ***globally integrated group*** with a continued strong market position that is the go-to commercial partner in pain, attracting biotech, start-up and VC partners
- Maintain and capitalise on our closely-coordinated regional structure, allowing us to be ***nimble and agile in regional commercial execution***

DRAFT

As leaders in pain, we must expand our offering beyond just a me
short of being a full service pain management company

GDC comment: some of these make up a continuum, but not all – for example, why devices where it is? Objective measures of pain and pain apps, too, can help support pain medicines or help build disease management programs. Some of these are tools and some are pardigms



Alix: I would add Diagnostics and subsume: Biomarkers, measures of pain

Pain intervention
Patient centric support
Scientific development

DRAFT

To achieve our vision, we must deliver on critical strategic imperatives

Our strategic imperatives:

1. **Optimise our current business**
2. **Innovate in pain**
3. **Build a diverse portfolio**
4. **Develop the right operational model**

Agenda

1 **The pain therapy landscape**

2 **Our vision**

3 **Our plan**

GT – add tracker

We have developed a plan of action to achieve our strategic imperatives

Our strategic imperatives:

1. **Optimise our current business**
2. **Innovate in pain**
3. **Build a diverse portfolio**
4. **Develop the right operational model**

DRAFT

We must optimise our current assets to ensure we have the base from which we can grow

DRAFT

1- OPTIMISE

DRAFT

1- OPTIMISE

We will protect our ADF portfolio through legislation and investment, whilst opportunistically seeking novel opioid approaches that eliminate the need for ADF

Advantages of ADFs

Market forecast

Alix: why would we actively seek novel opioid approaches over new MOAs. Seems that our focus should be on non-opioid approaches no matter the SE profile

Disadva

Limitations of

Payors and physicians often don't recognise the benefit

The ADF market is highly competitive

LEK:

David will work on this slide – provide an update

Our approach to ADFs

1 Optimise our current opioid portfolio and support the value of ADFs through policy and legislative advancement

2 Selectively invest in assets that help protect ADF portfolio

3 Pursue novel opioid approaches that eliminate or significantly reduce the potential for abuse

Source: GBI Research

DRAFT

1- OPTIMISE

In the future, our opioid business faces risks across geographies that need to be managed appropriately in order to be mitigated

	Description	Timeframe
Developed markets	Increasing pressure on pricing and need to demonstrate value over generics. Limited perceived value of ADFs	Mid
	Patent expiration of key products	Short
	Grunenthal and Teva rebuilding in pain	Mid
	Negative public opinion and anti-opioid publicity	Short
	U.S opioid guideline changes impacting prescription habits globally	Mid
Emerging markets	Poor clinical infrastructure; treating pain is low priority	Long
	Pricing pressure of emerging universal health systems	Mid
	Regulatory and guideline restrictions on pain medications	Short
	Cultural barriers to pain treatment	Mid

LEK:

To back-up or David to rework story as is too detailed

oaches

ovative

into

Market Access

Competitive

- Pursue BD opportunities to expand portfolio and become partner of choice
- Look for LCM opportunities within current portfolio

Cultural

- Communicating the importance of pain management
- Identify opportunities drive correct use of opioids/guidelines with KOLs

Risk level: High Medium Lower

DRAFT

1- OPTIMISE

There are several additional activities to optimise the core opioid business to support our pipeline expansion

FOR CORE TEAM DISCUSSION

LEK:

David will work on this slide – provide an update

pportunities

innovate LCM approaches

unities in our pipeline

ll key governmental and

e.g. US opioid restrictions)

Defend against generics	
Address potential access restrictions	
Leverage best marketing practices	• Innovative marketing approaches around the patient journey
Expand geographically	• Continuing to launch existing portfolio across the globe
Develop business opportunistically	• Pursuing differentiating opioid opportunities (e.g. next-generation opioids, promising ADFs)
Work together globally	• Creating global synergies through global working SOPs and consistent global branding

Protect the core Grow the core

DRAFT

We have developed a plan of action to achieve our strategic imperatives

Our strategic imperatives:

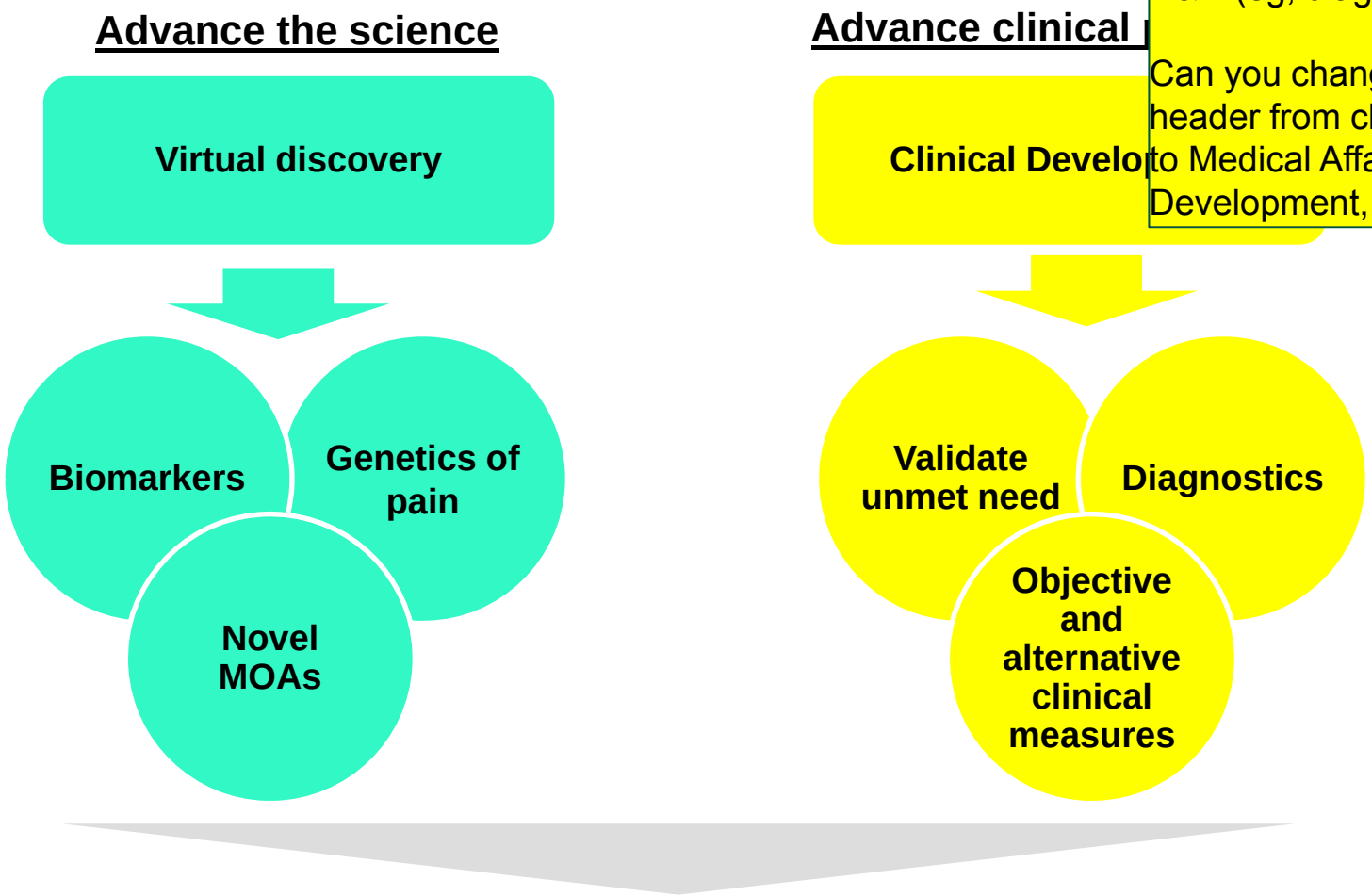
1. Optimise our current business
2. **Innovate in pain**
3. Build a diverse portfolio
4. Develop the right operational model

DRAFT

We will innovate by partnering with external experts to advance th pain and uncover new ways of solving the pain problem

GDC comment: much of what is in yellow is either strictly medical affairs (validate unmet medical needs, for example) while others are shared medical and clinical R&D (eg, diagnostics, PROs).

Can you change the square header from clinical development to Medical Affairs and Clinical Development, please.



1st Purdue/Mundipharma Global Pain Advis er 2016

Alix: I would say --- placeholder for Global Pain Advisory Board --- as we are working on logistics now

DRAFT

2- INNOVATE

We are not proposing to re-build a research organisation in-house, but to expand ongoing efforts to establish a virtual discovery model

GDC comment: as discussed at the EC, we may be missing something by not doing something brave here. For pain, why not have a single BD and single R&D organization? Why not have a scientific value-evidence global group for pain?

Steps for working in a discovery model

Establish an **independent team**

↓

Define the **ideal mix of MOAs & indications** to target

↓

Establish network of KOLs & partners to support candidate selection & actually do the lab/early clinical work

↓

Scout for candidates that match our desired portfolio

↓

Structure the partnership innovatively to increase PoS/ minimise risk

DRAFT

2- *INNOVATE*

We will innovate by partnering with external experts to advance the understanding of pain and uncover new ways of solving the pain problem

Biomarkers

- Identification of biom
development of sign
responders/non-res

R&D to validate

Petra/Alexander/Thomas: Please c
what we are thinking exactly for sig
confirm you are happy with these 3
level buckets

GDC comment: validation of serotonin is interesting but maybe too narrow; it is one of several proposals on the table.

How do we build into this, too, some of the interesting work beyond R&D into the practice spectrum, eg, wearables, predictive analytics, etc

Genetics of pain

- Identification of fibromyalgia sub-populations (phenotyping) to enhance disease understanding and identification of targets

→ **Validation of serotonin hypothesis for FMS**

Novel MOAs

- Work with research labs to identify the mechanisms behind pain sensation and identify and develop novel targets

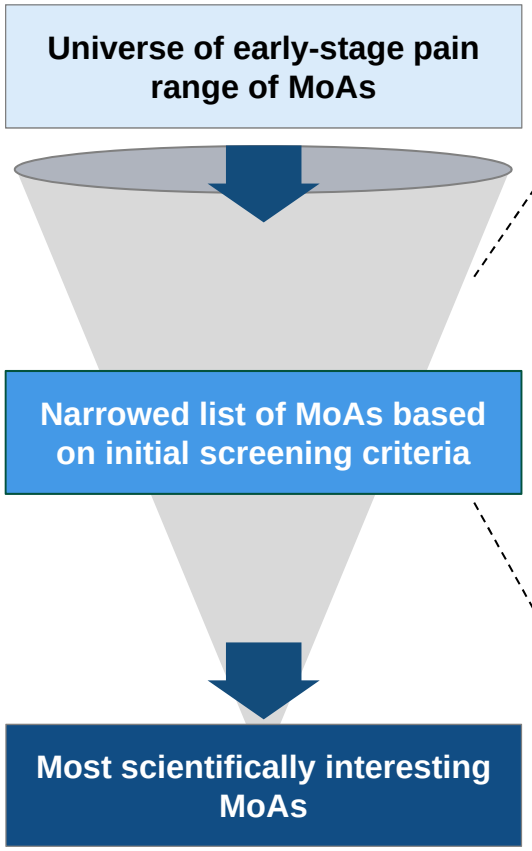
→ **Mapping & prioritisation of universe of pain MoAs***

**See next slides*

DRAFT

A screen of the universe of early-stage pain MoAs to identify the most promising MoAs not currently in our pipeline has been completed

MoA shortlisting process



Key step	Description
• Development of long list of MoAs and initial triage of list	• Deprioritized unattractive MoAs based on key triage criteria • Clustered MoAs based on biological targets
• Identification of the most attractive areas ***Key MoA clusters***: 1. Opioids 2. Ion channels 3. Neurotransmitter modulators 4. Anti-inflammatories 5. Cannabinoid modulators	• Selected the most interesting clusters of MoAs • Landed on five key clusters of MoAs • Identified novel / differentiated therapeutic approaches within these clusters
• Prioritization and review of attractive MoAs within key clusters	• Following deep dive profiling of the most attractive MoAs, produced a final list with high, second and third priority attractive MoAs • Focused on MoA that we are not already pursuing to identify opportunities to augment our pipeline

DRAFT

2- INNOVATE

We will focus on several promising MoAs that may offer greater efficacy and fewer side effects while considering interesting products that fulfil these criteria

We are already pursuing several promising novel MoAs

- **Sigma-1 antagonists**
  - Effective analgesia without opioid-related side effects
- **TRKA inhibitors**
  - Strong, targeted efficacy in addressing pain
- **CGRP antagonists**
  - Quick, efficacious and long lasting migraine relief
- **TRPV1 antagonists**
  - Fewer side effects related to hyperthermia
- **DHODH**
  - Less abuse potential

We have also identified several more attractive MoAs

- **Biased opioid agonists**
  - Less addictive, fewer side effects
- **$Na_v1.7/1.8$ inhibitors**
  - Effective analgesia with fewer side effects
- **TRPA1 antagonists**
  - Fewer side effects related to hyperthermia
- **$GABA_A$ $\alpha2/\alpha3$ PAM***
  - Dual effects on emotions and pain, fewer side effects
- **NMDA-NR2B antagonists**
  - Fewer side effects
- **mGluR5 NAM***
  - Adjunctive to SSRIs / SNRIs

Note: * PAM: positive allosteric modulator; NAM: negative allosteric modulator.

2 INNOVATE

DRAFT

We will innovate by partnering with external experts to advance t pain and uncover new ways of solving the pain problem

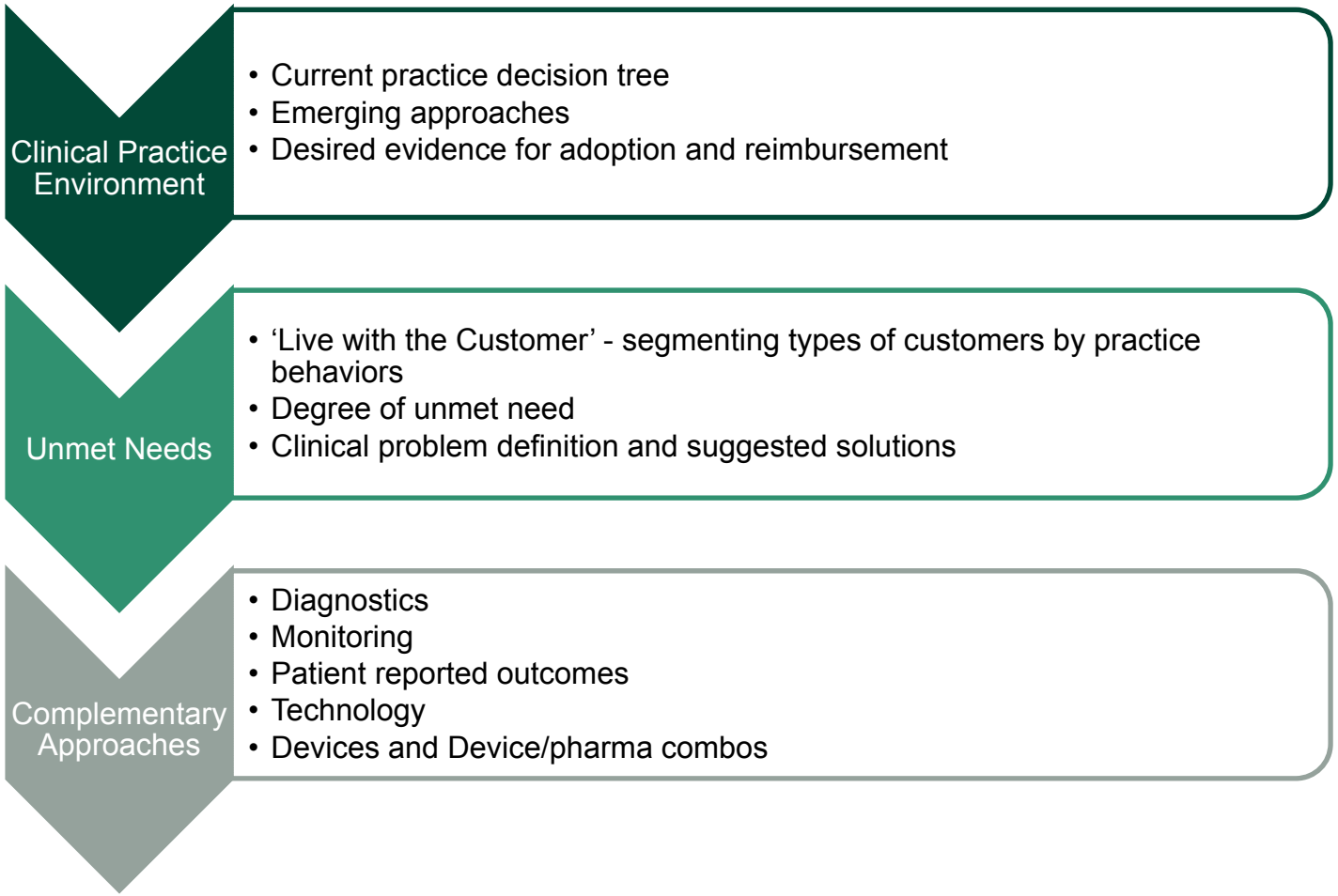
GDC comment: from a US perspective, much of this is within medical affairs; we would want to add quite a bit to this one. Suggest that medical affairs can recreate this one for you.

Uncover and Validate unmet need	• Deep insights into the unmet needs in pain, to select a prioritised list of target indications	**Assessment and prioritisation of pain indications** **See next slides*
Diagnostics, Metrics/ PROs, and Monitoring	• Emerging diagnostics, patient outcome measures, pain monitoring approaches	**US: Digital LEK Project - ongoing**
Disrupting pharma approaches: Device, Combos	• Work with Clinical KOLs on developing disruptive technologies to add to the Rx in their armamentarium	• Trauma AUC measures for Penthrox • *PRO work - tbc*

Work-in-Progress

DRAFT

We will innovate by partnering with external experts to advance the understanding of pain and uncover new ways of solving the pain problem



Medical Affairs optimizes the healthcare value story across the product lifecycle

DRAFT

2- INNOVATE

To determine which indications could be attractive to pursue, we have assessed key pain indications, focusing on the degree of unmet need and scientific validation

Relative weight of criteria

Degree of unmet need
- Availability of therapies to manage the disease
- Level and type of unmet needs

High Medium Low

Understanding of disease & treatment
- Level of understanding of disease pathology
- Rationale for treatment approach

High Medium Low

Market opportunity
- Size of prevalent population
- Attractiveness to payors

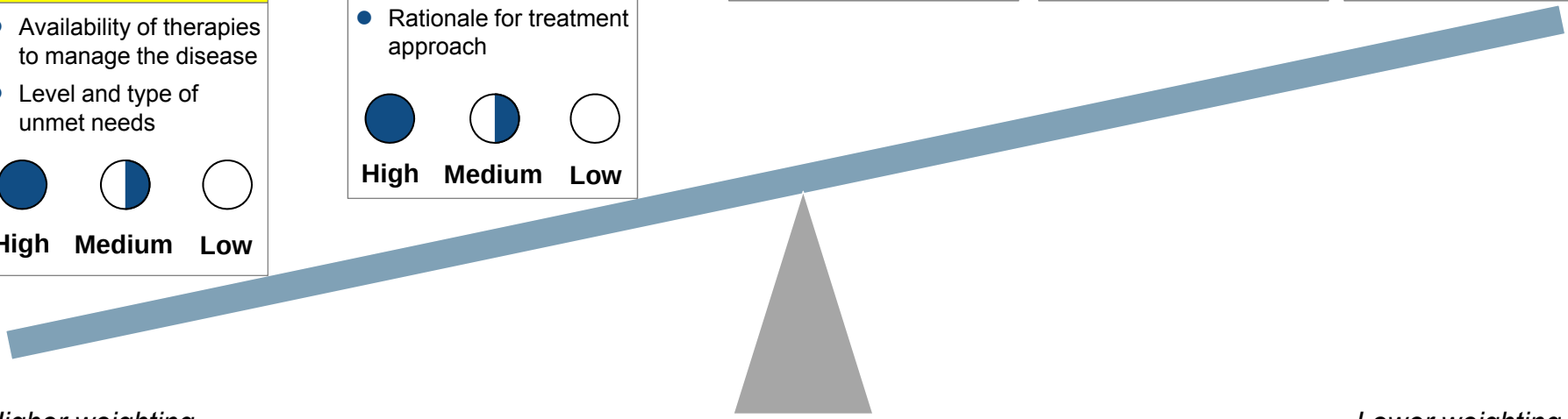
High Medium Low

Competitive intensity
- Number of marketed products
- Number of pipeline products

Low Medium High

Probability of clinical trial success
- Level of establishment of trial endpoints
- Approval history and Phase III activity level

High Medium Low



Higher weighting

Lower weighting

Note: we will continue to refine format for final presentation

DRAFT

DRAFT

2- INNOVATE

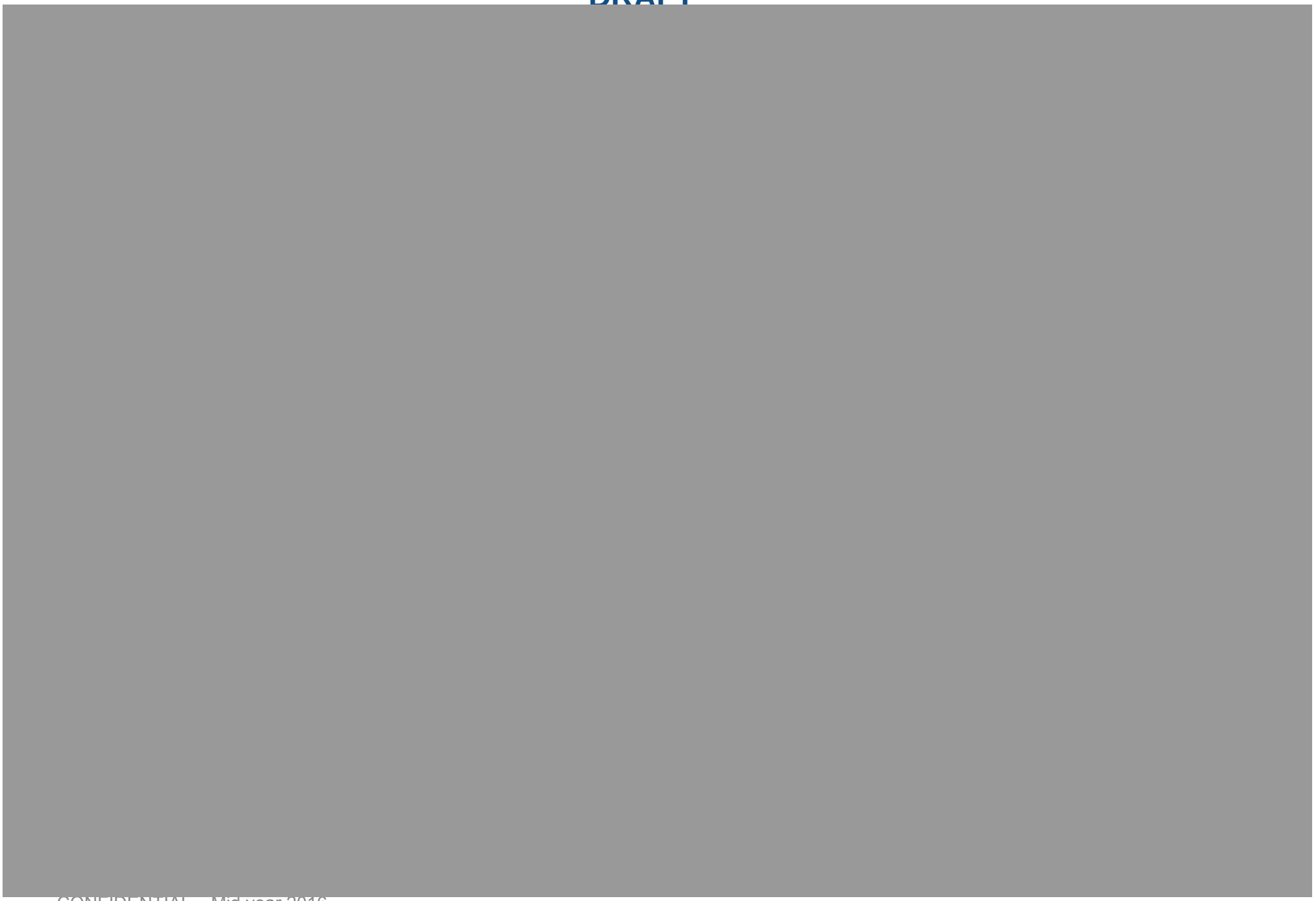
DRAFT

We have developed a plan of action to achieve our strategic imperatives

Our strategic imperatives:

1. Optimise our current business
2. Innovate in pain
3. **Build a diverse portfolio**
4. Develop the right operational model

DRAFT



2015 DATA

Bup/Oxy to be included when forecast is received

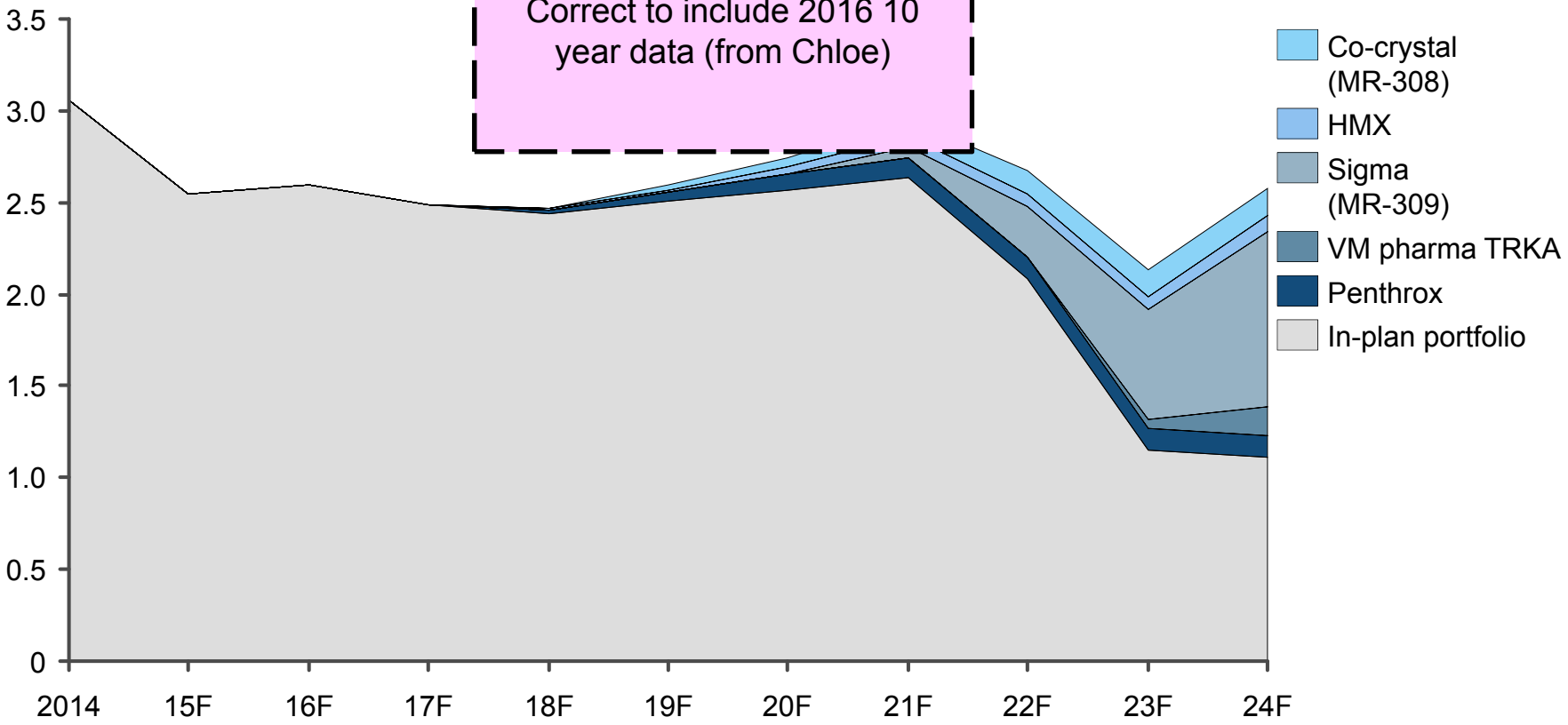
As it currently stands, our current pain portfolio is not sufficient to support our long-term growth

LEK

Align format to this year's

Correct to include 2016 10 year data (from Chloe)

Global Pain portfolio net sales (2014-24F)
Billions of dollars



Note: * Forecasts for EU region from 2015F to 2021F are from Nov 2014

DRAFT

When selecting and developing assets in pain, we will ensure each asset fulfills specific criteria

Superior clinical outcomes

Products that boast meaningful clinical benefit

Market exclusivity

Products protected in the geographies we market in

Ability to register, import, sell

Products we can successfully commercialise

Potential for new indications and formulations

Products we can continue to develop

MOA, phase & geographic balance & diversity

Products that add up to a balanced & diversified portfolio

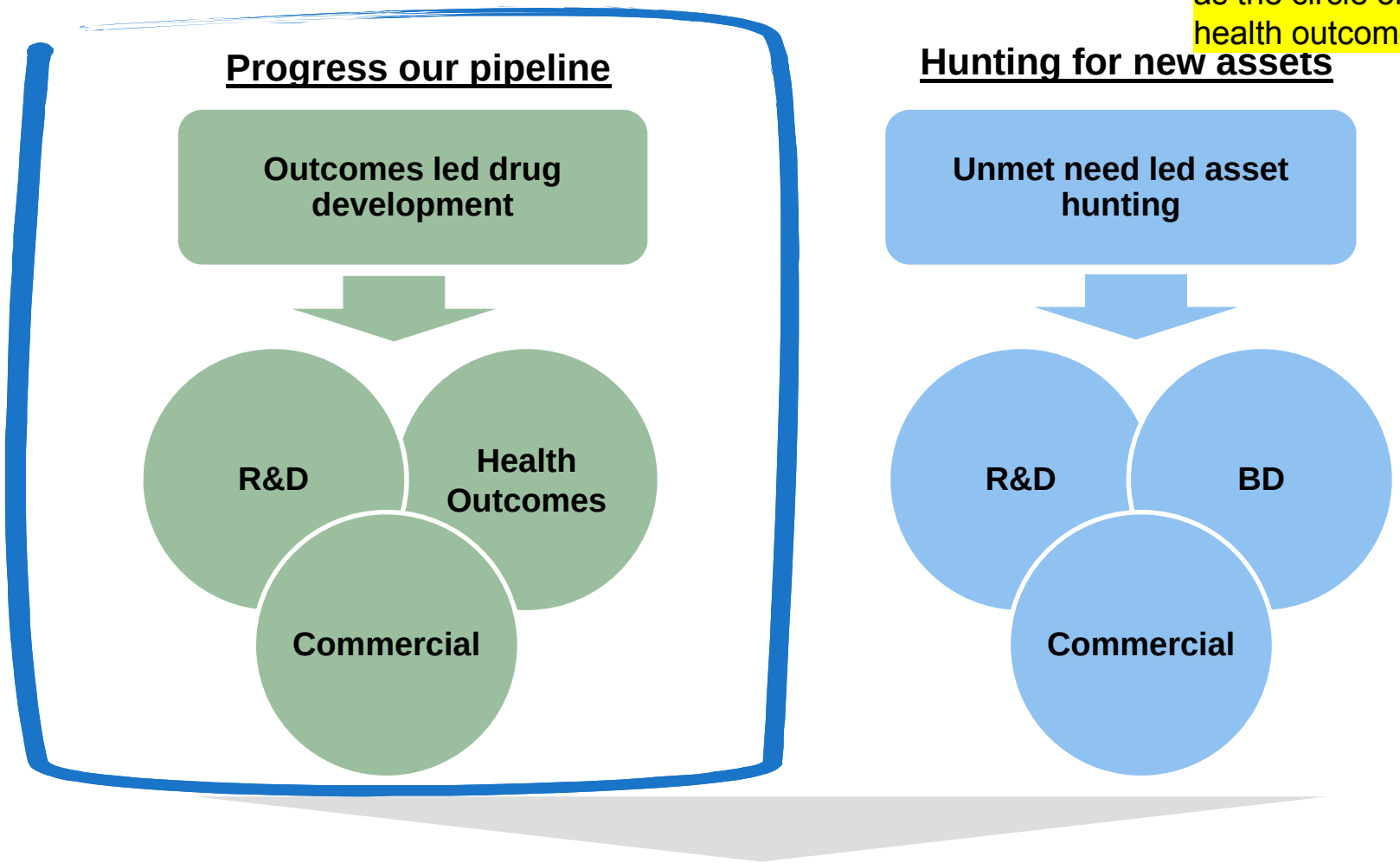
Alix: will the landscape include the possibility of other pain management --- Neuromodulation --- SCS and PNS for example. I would suggest that it does as they are picking up steam in US

DRAFT

3- BUILD

We will continue to build a diverse portfolio by progressing our current pipeline and by aggressively hunting for new assets

GDC comment: what happened to medical affairs? Can we have this as the circle on the right instead of health outcomes?



Asset-led global cooperation & governance

DRAFT

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region:

DRAFT

DRAFT

DRAFT

Kate's team (Nick Lagan) to provide

To provide further Penthrox update slides

1. CSFs
2. Trauma pain 2nd DCP timelines
3. Procedures study design & 2nd DCP scenarios
4. Long term strategy map
5. Evidence generation plans
6. Launch plans
7. Publications plan

DRAFT

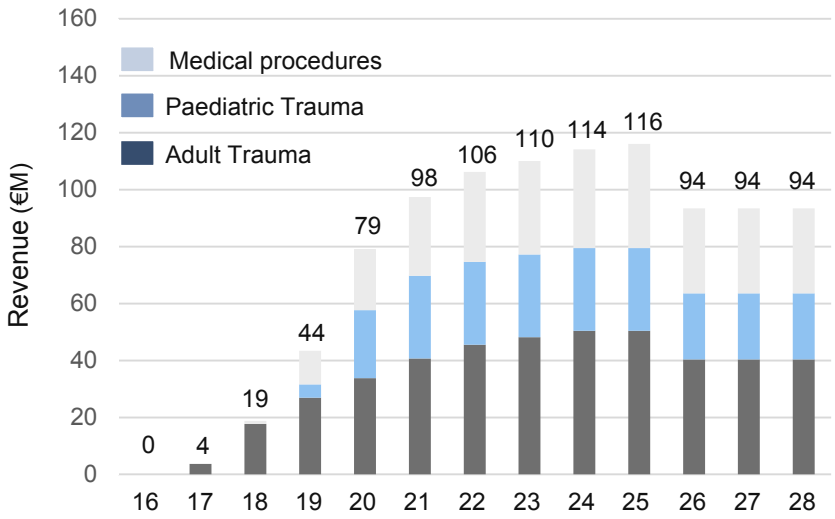
Kate's team (Nick Lagan):

To update/correct

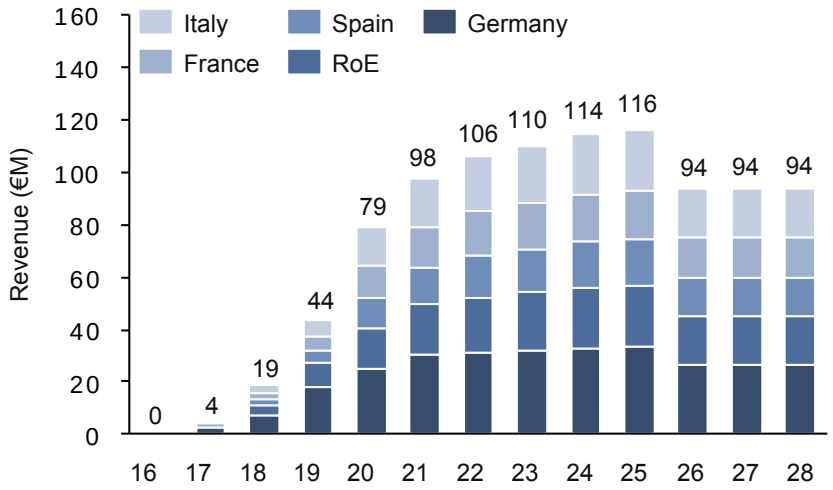
Penthrox methoxyflurane

2025 after launch in 2016 and subsequent LCM

by Indication (€M)



EU Revenue Forecast by Region (€M)



Key Assumptions			
Launch average net selling price	€11	Paediatric trauma pain – Walk-In peak share	30%
Adult trauma pain – Walk-In peak share	Average ~18% (16% - 24%)	Paediatric trauma pain – Ambulance peak share	50%
Adult trauma pain – Ambulance peak share	30%	Medical procedures peak share	30%

* Assuming LOE year is 2025 and generic entry is 2026

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region:

DRAFT

CTC Brand Fundamentals

- **CTC = co-crystal of tran**
- **Essence: Stren**
- **Positioning:**
  - **FOR (Target audien**
  - **WHO WANT (Need /**
  - **PENTHROX IS (Fra**
  - **WHICH OFFERS (P**
  - **FOR (Target audien**

Kate's team (Galia Reicher) to provide

To provide further CTC update slides

1. CSFs
2. Overall launch timelines in all countries
3. Phase III study designs & sites
4. Pricing work planned
5. Demand work planned
6. Publications plan
7. Ad board

DRAFT

Progressing our pipeline: Asset strategies and updates

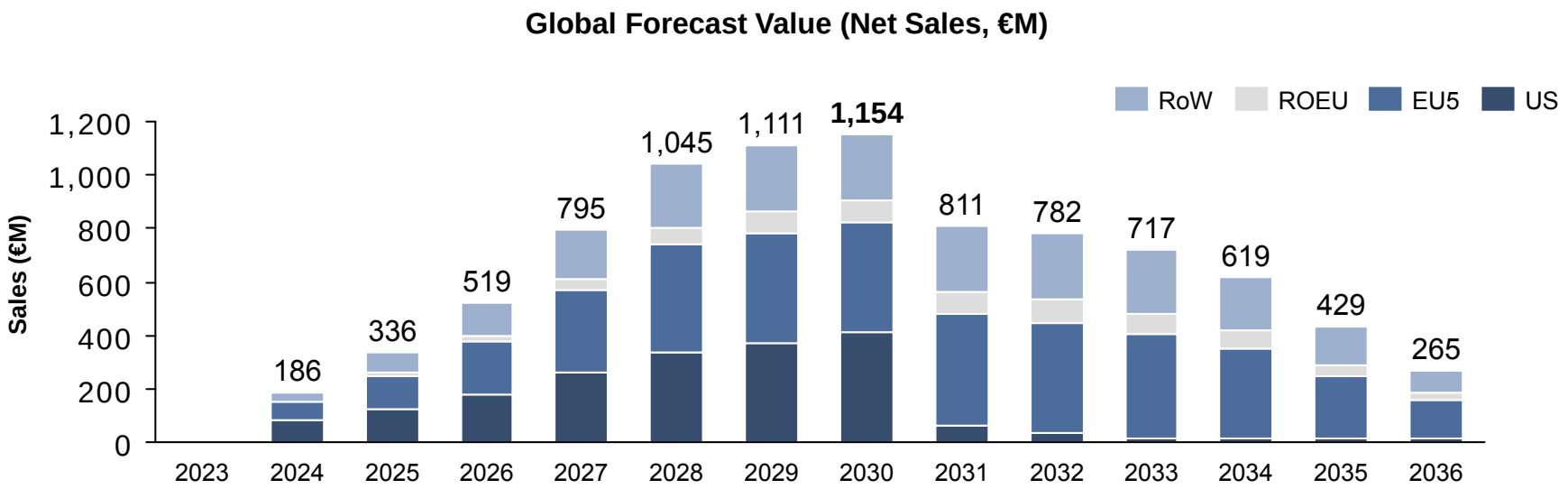
1. Penthrox
2. Co-crystal
3. **Sigma**
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region:

DRAFT

Base Case – Neuropathic Pain

Global sales projected to peak at ~€1.2B in 2030

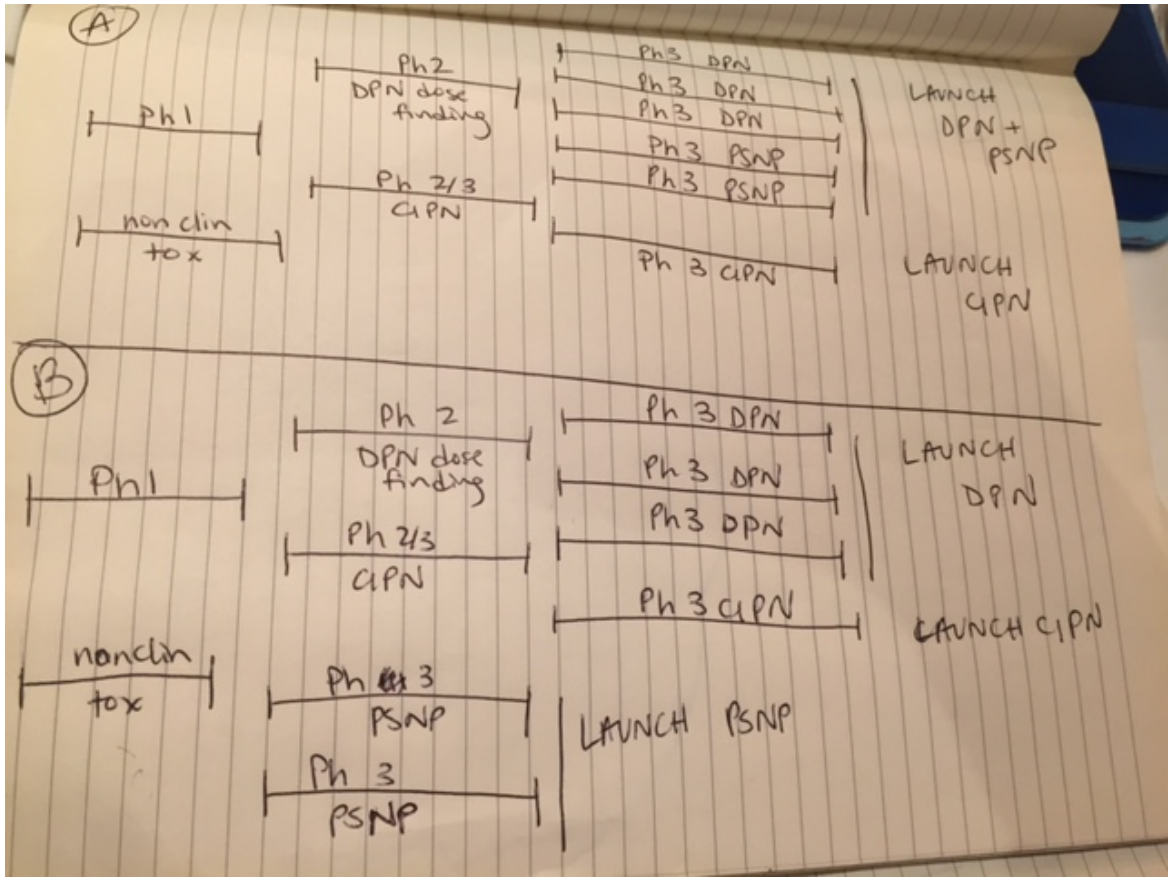


Key Assumptions

Launch/ LOE	• **EU:** 2024 / 2033 • **US:** 2024 / 2030 • **ROW:** 2024 / 2033	• Efficacy superiority vs. Lyrica is likely • The price premium achievable over Lyrica will be sufficient to make a compelling business case (e.g. premium over a Gx) • Market share taken from incumbent brands and from generic pregabalin / other anti-epileptics • The safety & tolerability profile will be acceptable

Format to be converted

sigma



Petra

Let's discuss which slides from the BDC/STC (if any) we should include

DRAFT

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. **TRKA**
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

DRAFT

Christian Darland /Andy Albright

To provide further TRKA update slides:

1. Overall timelines
2. Structure of development programme
3. Scenarios / decision model
4. Forecast

DRAFT

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

HMX

Kate's team (Fabio Kellett) to provide

To provide HMX slides

1. Decision tree, scenarios & financials
2. Phase III design
3. Countries feedback/forecast/
4. Next steps

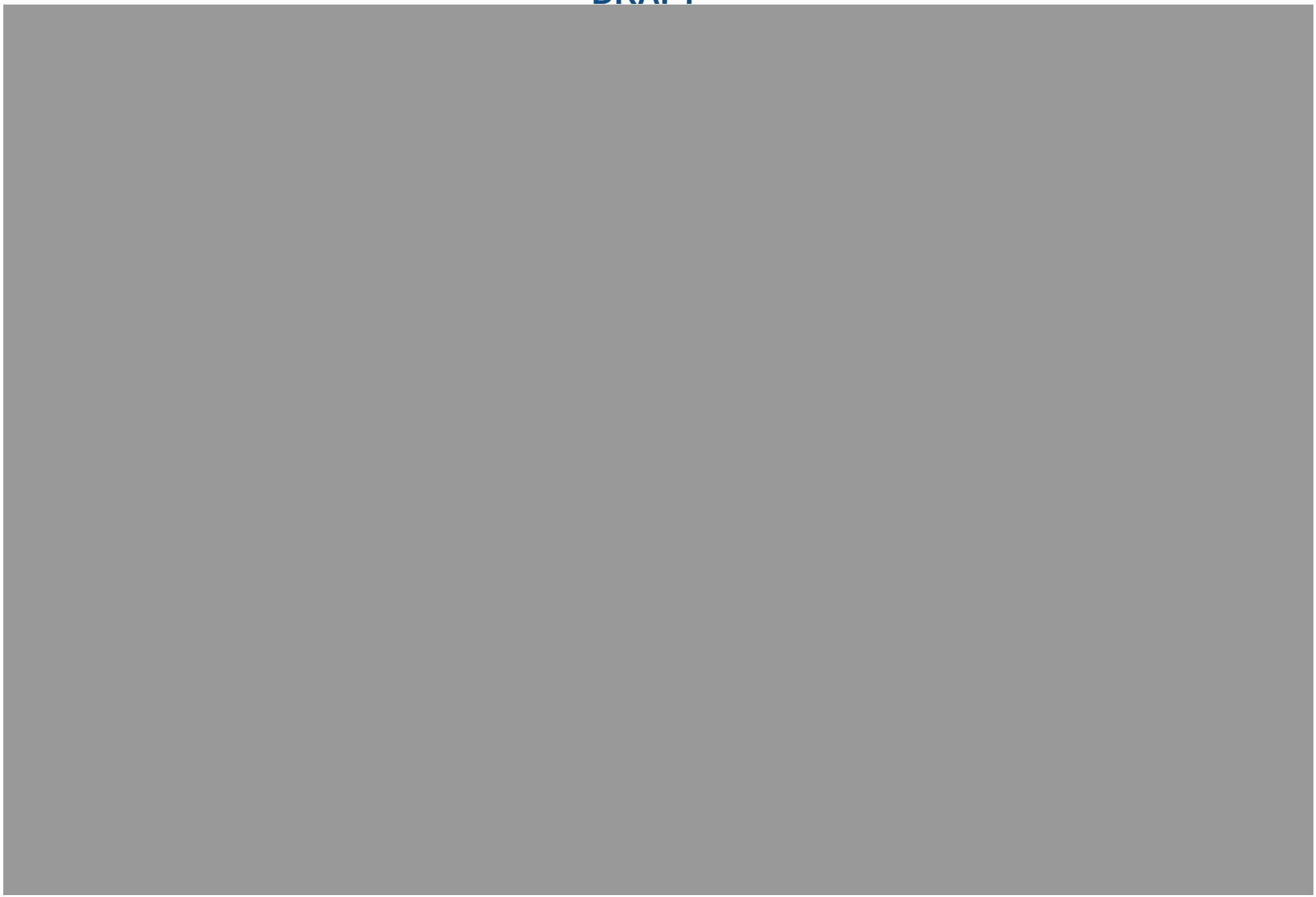
DRAFT

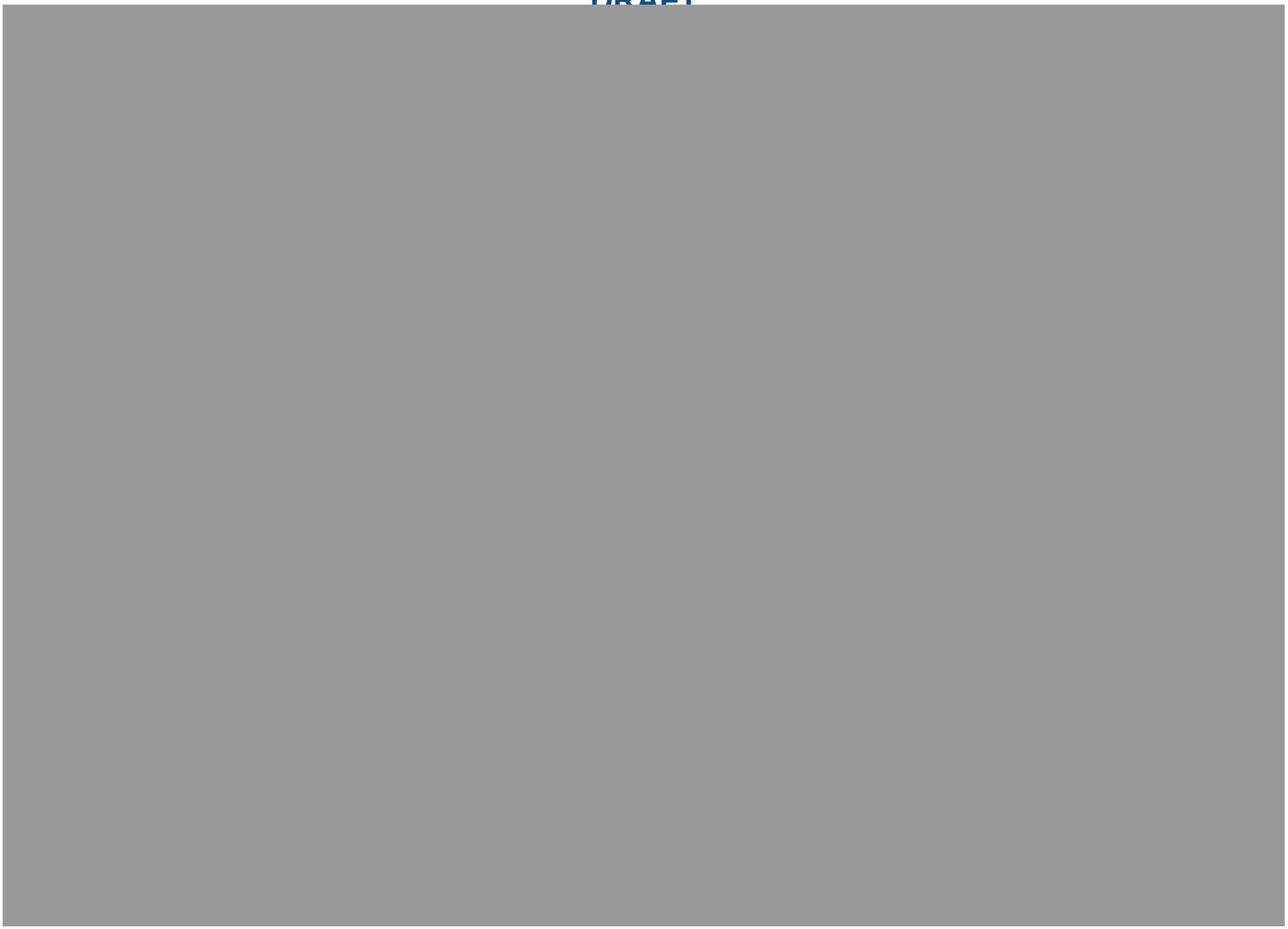
Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. **BOX (Bup/Oxy)**
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region: 

DRAFT





DRAFT

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region:

DRAFT

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region:

DRAFT

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region:

DRAFT

DRAFT

Progressing our pipeline: Asset strategies and updates

1. Penthrox
2. Co-crystal
3. Sigma
4. TRKA
5. HMX
6. BOX (Bup/Oxy)
7. MSR
8. Hysingla
9. Hydrolox
10. Anabios

Lead region: 

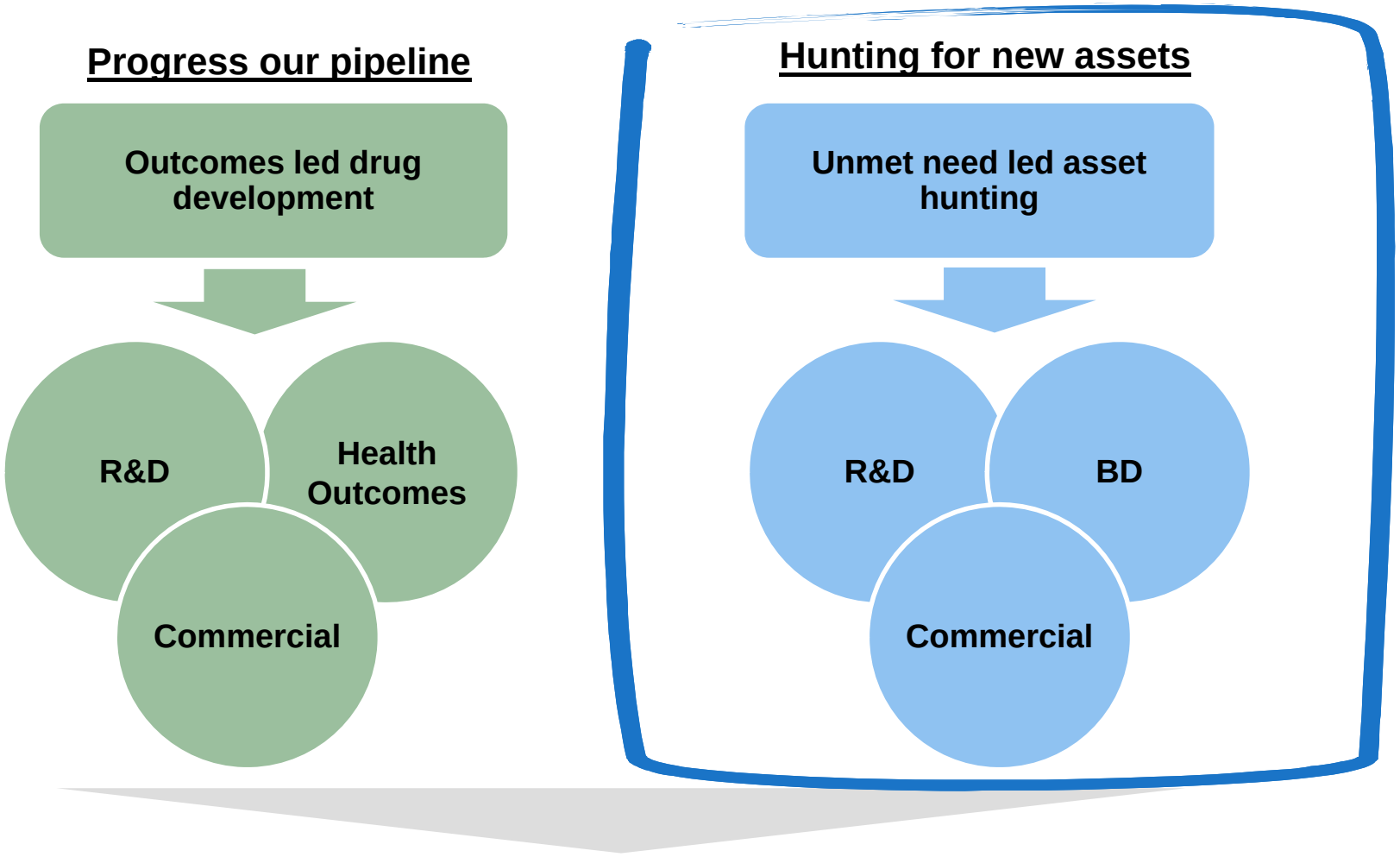
DRAFT

DRAFT

3- BUILD

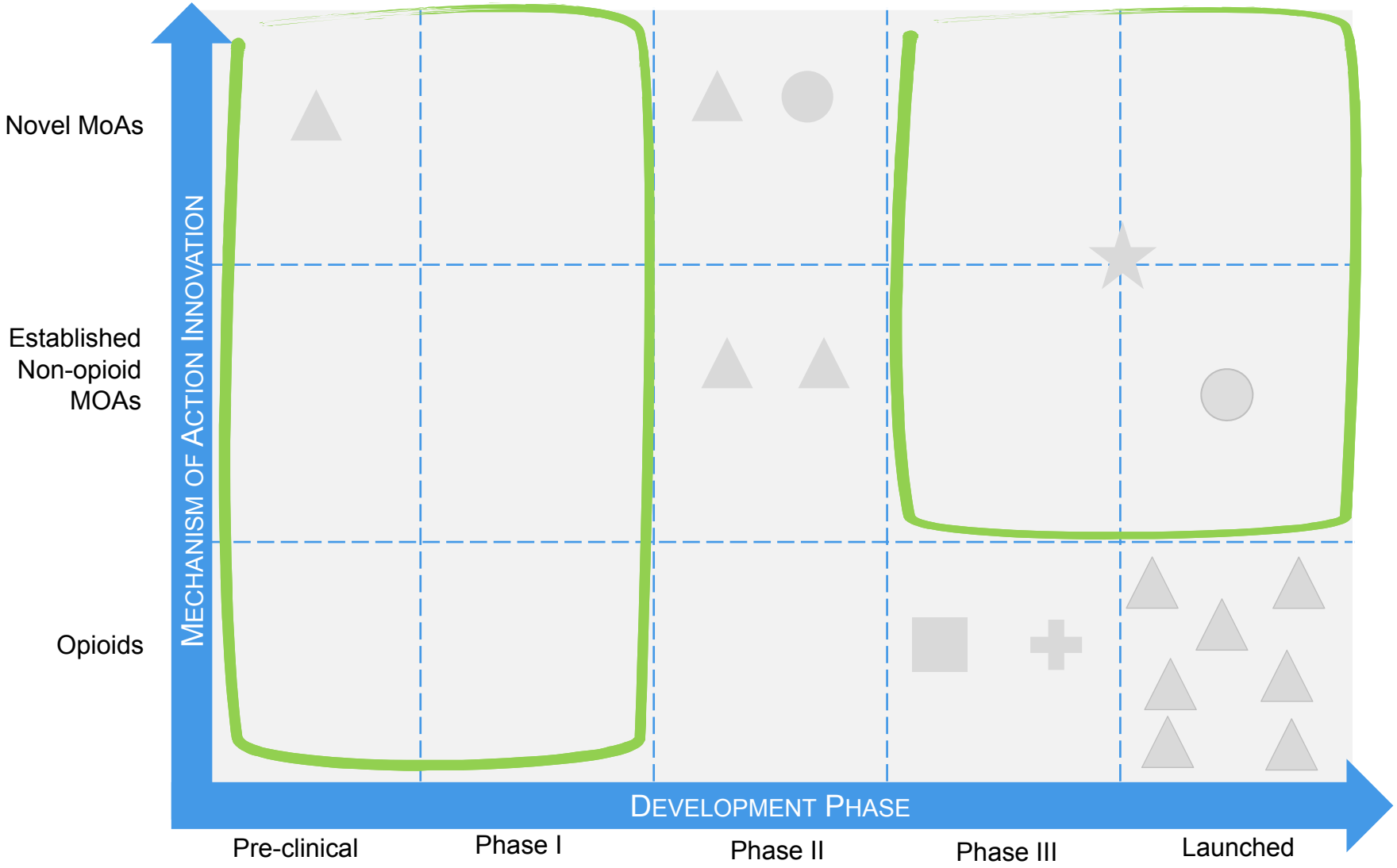
We will continue to build a diverse portfolio by progressing our current pipeline and by aggressively hunting for new assets

GDC comment: Medical Affairs instead of health outcomes



DRAFT

Hunting for new assets – we must fill the gaps in our pipeline if we want to achieve our vision of becoming leaders in pain

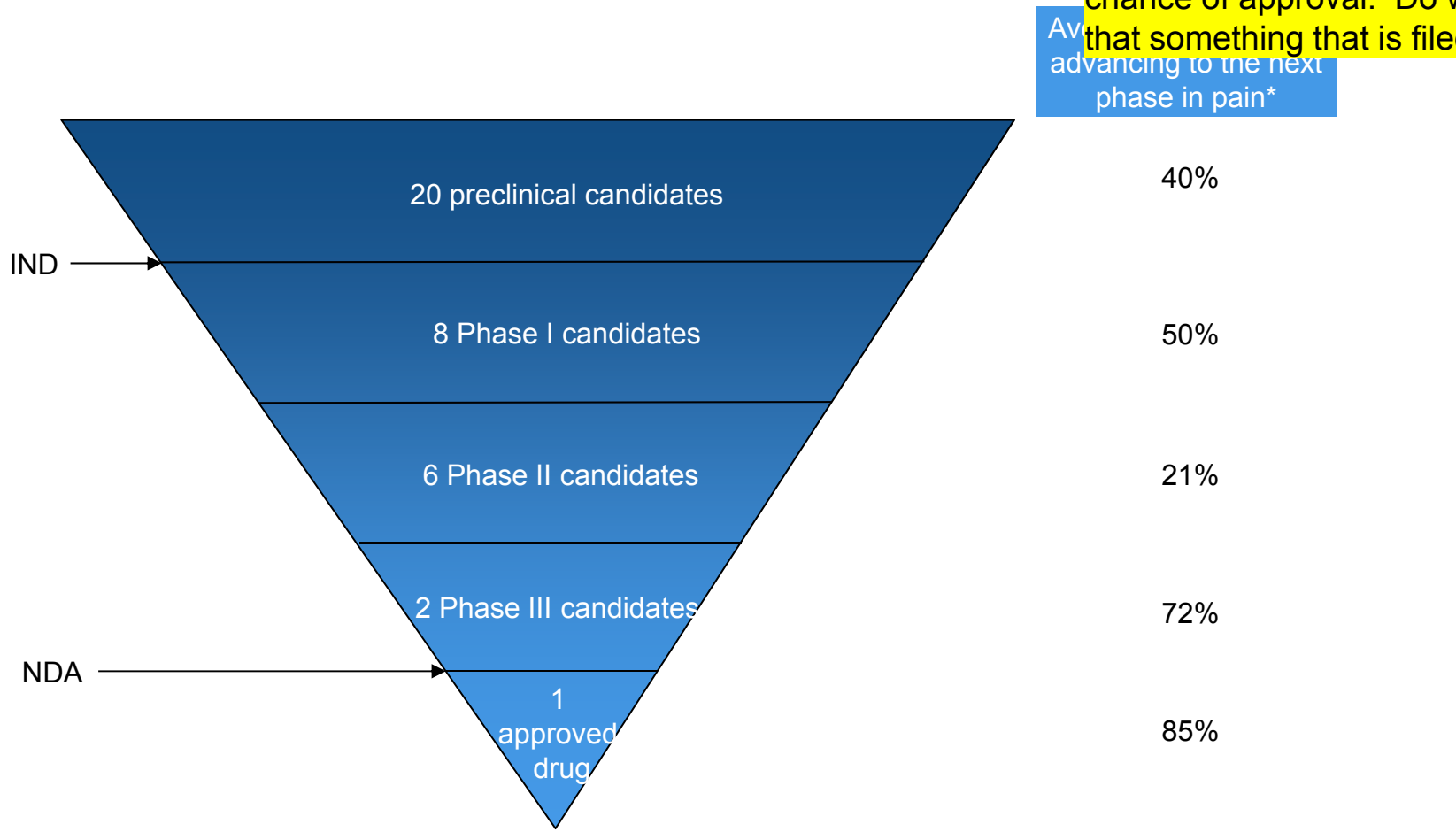


Source: Mundipharma & Purdue

Note: assessment of TA leader probability-of-success is still ongoing

To help define our expansion from the core into new products, we have looked at the probability of success for pain therapies at each stage of develop

GDC comment:something wrong if an approved product has 85% chance of approval. Do we mean that something that is filed?



The overall probability of success for a preclinical pain therapy is c.3%

Note: *Represents clinical probability of success for pain drugs in the U.S. in each stage (not cumulative), based on analysis of 2014-5 data from CenterWatch, Tufts database, BCG data, CRO database; Pain-specific data was not available for preclinical drugs, so a general estimate was compiled from PharmaProjects, *Drug Discovery World*, and FDA Review

DRAFT

3- BUILD

The new assets we pursue should be diversified across indications, MoAs and phases of development

We studied the pipelines of companies that are "TA leaders"…

- Celgene
  - Leader in oncology
  - Expanded from hematology-oncology into solid tumours and immunology
- Lundbeck
  - Leader in CNS
  - Deepened its portfolio in psychiatry while expanding into neurodegenerative and epilepsy treatments
- GILEAD
  - Leader in infectious diseases
  - Deepened its portfolio of HIV treatments and developed drugs against other infectious diseases
- novo nordisk®
  - Leader in metabolic diseases
  - Deepened its portfolio of diabetic treatments and expanded to haemophilia and other protein-based therapies

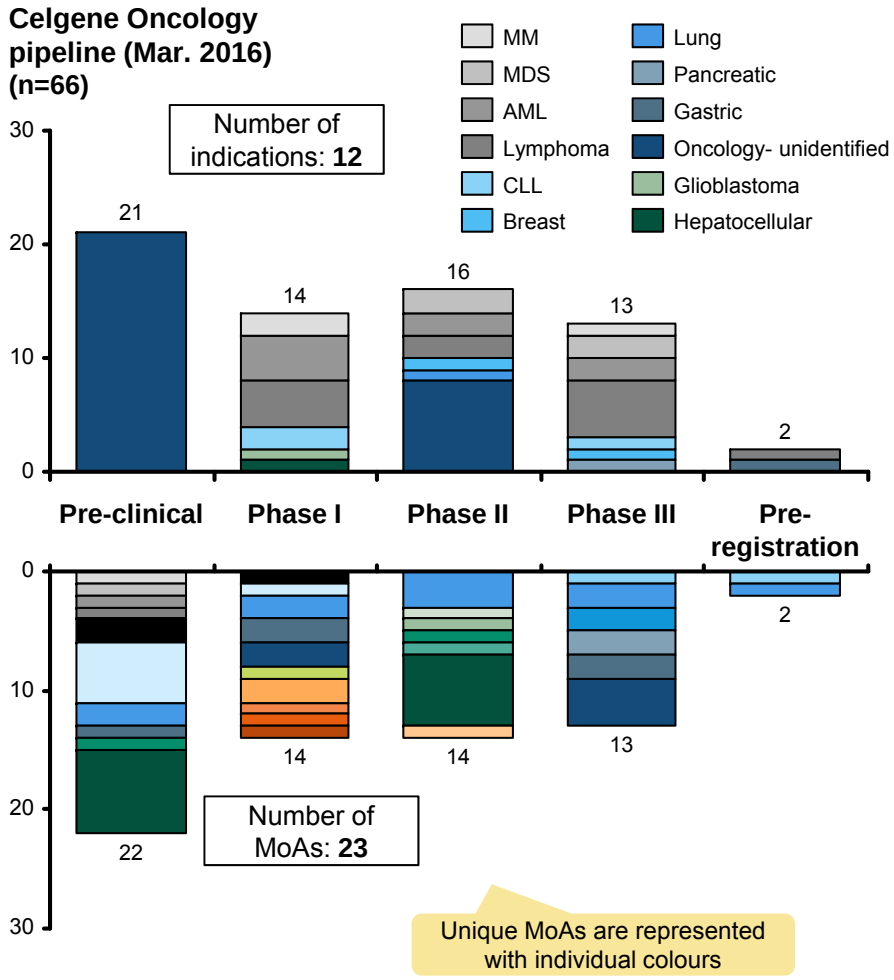
…to identify key common themes in a healthy and diverse pipeline

- Variety of indications in development
- Variety of MoAs and lines of therapy within indications
- Pipeline split evenly across different phases of development

DRAFT

3- BUILD

Case study: Celgene has developed a diverse oncology pipeline across indications, with a breadth of MoAs targeting multiple steps in carcinogenesis for each cancer



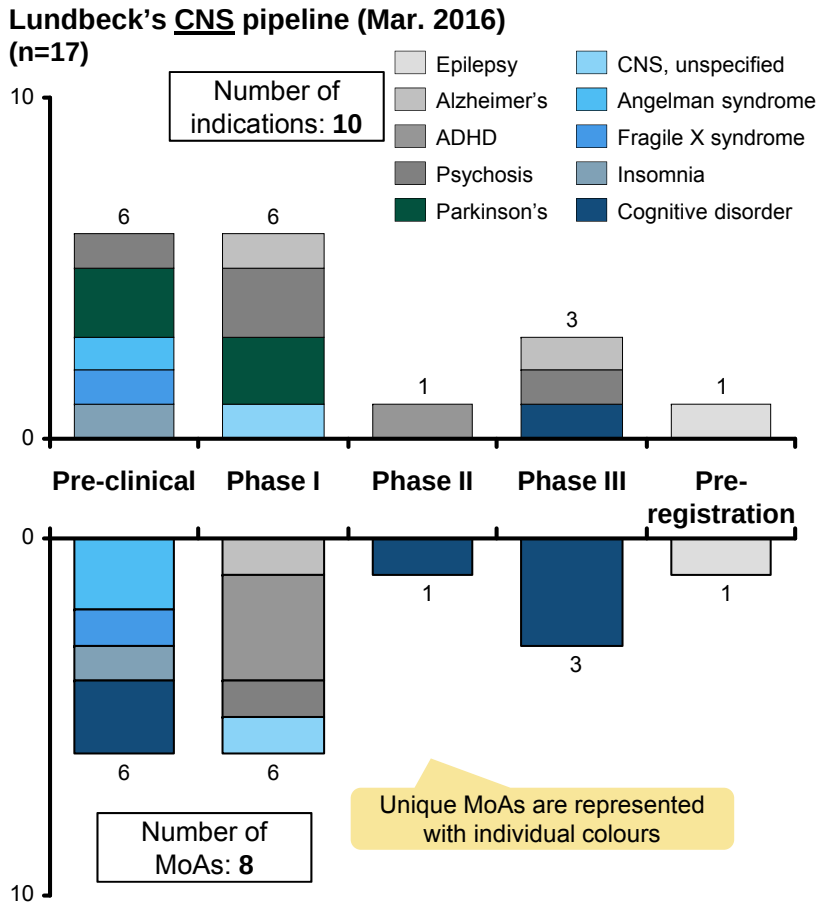
- Celgene's oncology pipeline has **evenly spread assets across all development stages**
  - **32%** of pipeline assets are in **preclinical** development, with **21% in Phase I and 24% in Phase II**
  - the **breadth of MoAs is very wide**; for most indications, **multiple steps within the pathway of carcinogenesis** are targeted
- Initially a small molecule cancer therapeutics company, Celgene **expanded its technology platform and disease focus through major acquisitions**, such as:
  - its acquisition of Pharmion in 2007 for $2.7B, through which it gained back all licences for Thalomid, widened its access to Europe and acquired Vidaza, a treatment for more severe MDS
  - its acquisition of Abraxis in 2010 for $2.9B, through which it acquired the blockbuster-potential drug Abraxane as well as a new platform, a nanoparticle albumin-bound technology
- Celgene has also **formed partnerships** with pharmaceutical companies in order **to enhance its portfolio**, for example:
  - through its partnership with Array BioPharma in 2007 for up to $500M, it gained access to two undisclosed new cancer and inflammatory disease targets
  - through its partnership with OncoMed in 2013 for $3.3B, it entered the space of stem cell cancer therapy
- In addition, Celgene has **continued to invest in internal R&D** in small molecules, inflammatory compound inhibitors and enzyme inhibitors, giving it the capacity to develop **compounds against multiple types of cancer targets**

Source: PharmaMedTechBI; PharmaProjects; Company website

DRAFT

3- BUILD

Case study: Lundbeck's pipeline spans key CNS indications with a spread of targeted MoAs



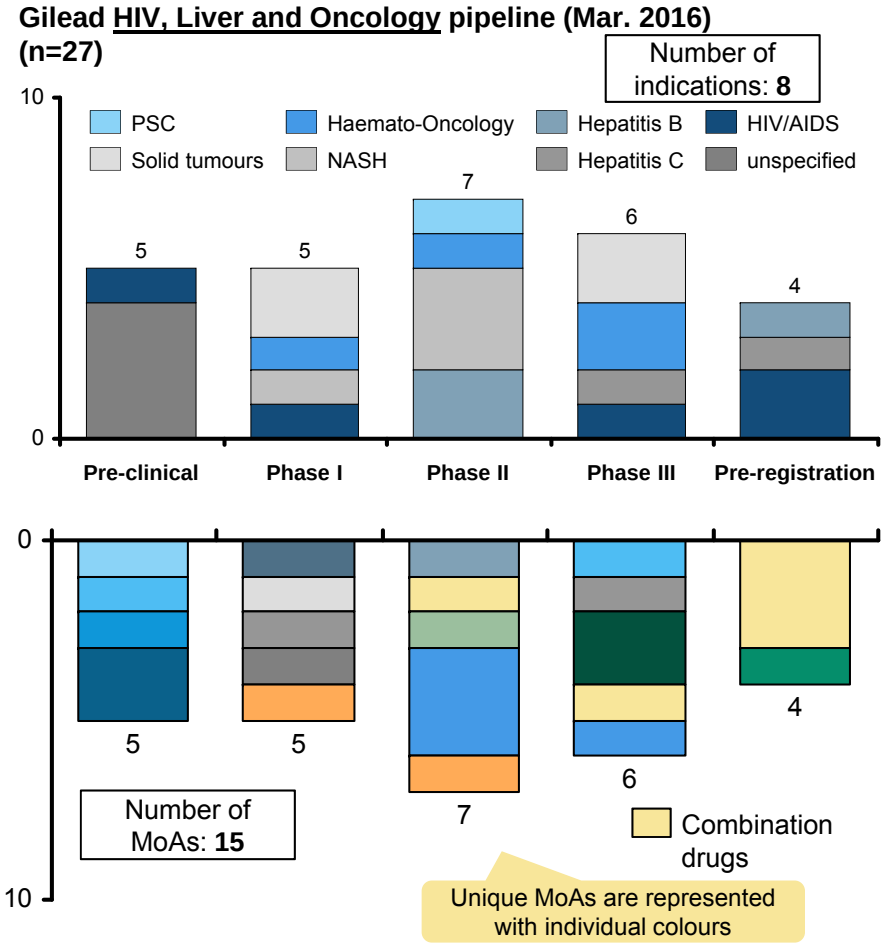
- Lundbeck's CNS pipeline has a **stronger presence in early development phases**, with 35% of the pipeline in preclinical development and another 35% in Phase I
- **The breadth of MoAs** (n=8) is **similar to the number of indications targeted** (n=10), due to the potential of drugs that alter neurotransmitter levels to affect multiple CNS indications
- Lundbeck's pipeline **developed through collaborations that led to product co-development**
- Takeda and Lundbeck co-developed Ph II and Ph I products
  - the Ph II product received approval as Brintellix and achieved sales of $0.6B in 2015
  - Lundbeck received $40M up front, $345 in development milestones and share of revenues as royalties. Takeda booked total sales and R&D costs
- Otsuka and Lundbeck **traded licences**;
  - Lundbeck received co-development and co-promotion of Ph III aripiprazole depot for the Americas, Europe and Australia; Otsuka received the option to co-develop and co-promote three of Lundbeck's undisclosed anti-psychotic agents after they have completed PhIIb
  - Lundbeck paid $200M up front, $1.2B in development and regulatory milestones and $400M in sales milestones. Lundbeck receives 50% of sales in Europe and Canada and 20% of U.S. sales
- Lundbeck also continued to **acquire strategic CNS assets via** M&A while **divesting a portfolio of non-core products** as part of its official strategy to **focus on newer, more strategic CNS products**

Source: PharmaMedTechBI; PharmaProjects; Company website

DRAFT

3- BUILD

Case study: Gilead's pipeline covers a large number of indications, utilising a wide breadth of MoAs



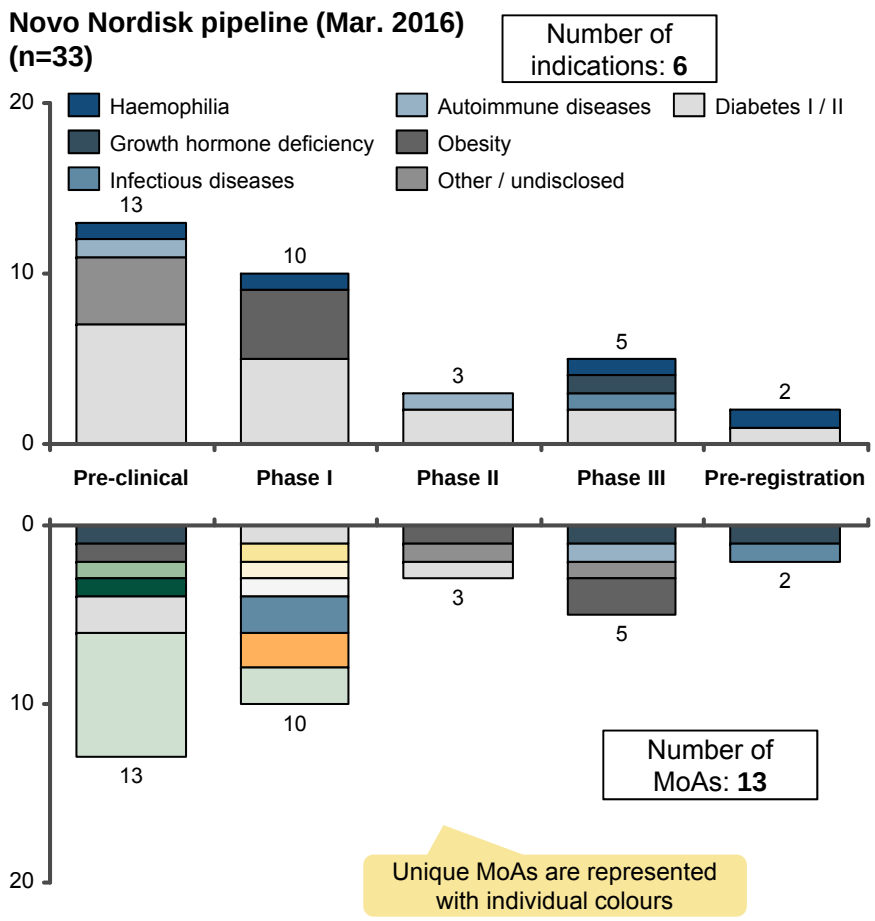
- Gilead's virology and oncology pipeline is **spread evenly across all phases**, with **20%** of the pipeline in **preclinical** development and **25% in Phase II**
- Gilead's pipeline includes a **larger number of MoAs** (n=15) than number of indications (n= 8), with **most MoAs in targeted development for only one indication**
- Gilead has shaped its current portfolio through the **acquisition of key assets**
  - it entered the HIV market through its merger with NeXstar in 1999 for $0.5B, which gave Gilead access to NeXstar's pipeline
  - Gilead entered the hepatitis C market by acquiring Pharmasset and its Ph III hepatitis C candidate for $11.2B
- Its portfolio of HIV and hepatitis drugs is dominated by **products acquired at late stages from collaborators**, e.g.:
  - emtricitabine from Tibotec
  - rilpivine from Janssen
- **Collaborations with large pharmaceutical companies** have also allowed Gilead to develop **new combination drugs**, such as Atripla, and enter developing markets

Source: PharmaMedTechBI; PharmaProjects; Company website

DRAFT

3- BUILD

Case study: Novo Nordisk's pipeline spans key metabolic conditions, such as diabetes and obesity



- Novo Nordisk's pipeline is focused in early-stage development, with **~70% of assets in preclinical or PhI development**
- Novo Nordisk is pursuing **more MoAs (n=13) than indications (n=6)**, with most **MoAs in targeted development for a specific indication**
- Novo Nordisk has **focused its internal R&D** on the development of insulin-based therapies, supplementing its internal manufacturing capabilities with **partnerships to access delivery technology**
  - Novo Nordisk **has leveraged its expertise in insulin delivery systems** to bring some of their most successful products to market, such as NovoRapid
  - their collaboration with Emisphere aims to co-develop oral diabetes treatments, focused on Victoza
- Novo Nordisk **expanded its portfolio with non-insulin diabetic products** and entered the market of protein-based therapies for haemophilia and other coagulopathies **through BD**
  - through its licensing of ZymoGenetics' recombinant Factor XIII for $70M it launched Tretten in 2012
  - through its acquisition of Neose for approx. $20M, Novo Nordisk gained access to recombinant Factor IX, currently in pre-registration for the treatment of Haemophilia B

Source: PharmaMedTechBI; PharmaProjects; Company website

Note: assessment ... -of-success is still ongoing

GT review

Note: WIP, analysis not yet final

All benchmarked companies used a mix of approaches to expand pipelines, de-risking early development and diversifying MoAs whilst remaining TA focused

In house R&D

- All companies have internal R&D functions that have produced key products, particularly in early growth phases

BD licencing

- In and out licencing used by all firms to ensure pipeline TA focus, diversify MoAs and increase pipeline assets post POC
- e.g. Gilead licencing products from collaborators late stage, NovoNordisk moving into non-insulin diabetic products, Lundbeck trading licenses with Otsuka

Partnerships

- Partnerships with development collaborators used to de-risk in PhI and provide later stage options
- e.g. Lundbeck co-development with Takeda, Gilead collaborating with big pharma for combination products, Celgene partnership with Array Biopharma

Acquisitions

- Acquisitions used mainly to acquire breakthrough technology and blockbuster potential assets in late phase development
- e.g. Gilead-Pharmasset, Celgene-Abraxis, Novo-Nordisk-Neose

Overall, companies aimed to:

- de-risk in early stages,
- remain MoA/Indication diversified through PhII
- place larger bets in late stages to maintain a steady flow of product launches

DRAFT

3- BUILD

[redacted]

How could we actually do this?

Pete M/ JJ

We need to add approx. costs to add that many products to our pipeline:

What are the approx. costs for:
1 x preclinical asset: cost of deal & cost of development
1 x phase 1 asset: cost of deal & cost of development
1 x phase 2 asset cost of deal & cost of development
1 x phase 3 asset cost of deal & cost of development

Allen/Ann

What type of creative structures could we come up with to make something like this a reality?

Alan/Petra

What type of R&D ideas would this make you think of – do we need to look at co-development options? Are there ways of doing some development virtually? Are there ways we can do more phase II/III adaptive design studies or earlier comparator studies to fail fast instead of waiting until later to get to “proof of relevance”?

Would we need to behave as a J&J type company but for R&D by asset or asset class with only loose ties centrally so that each can worry about their own asset?

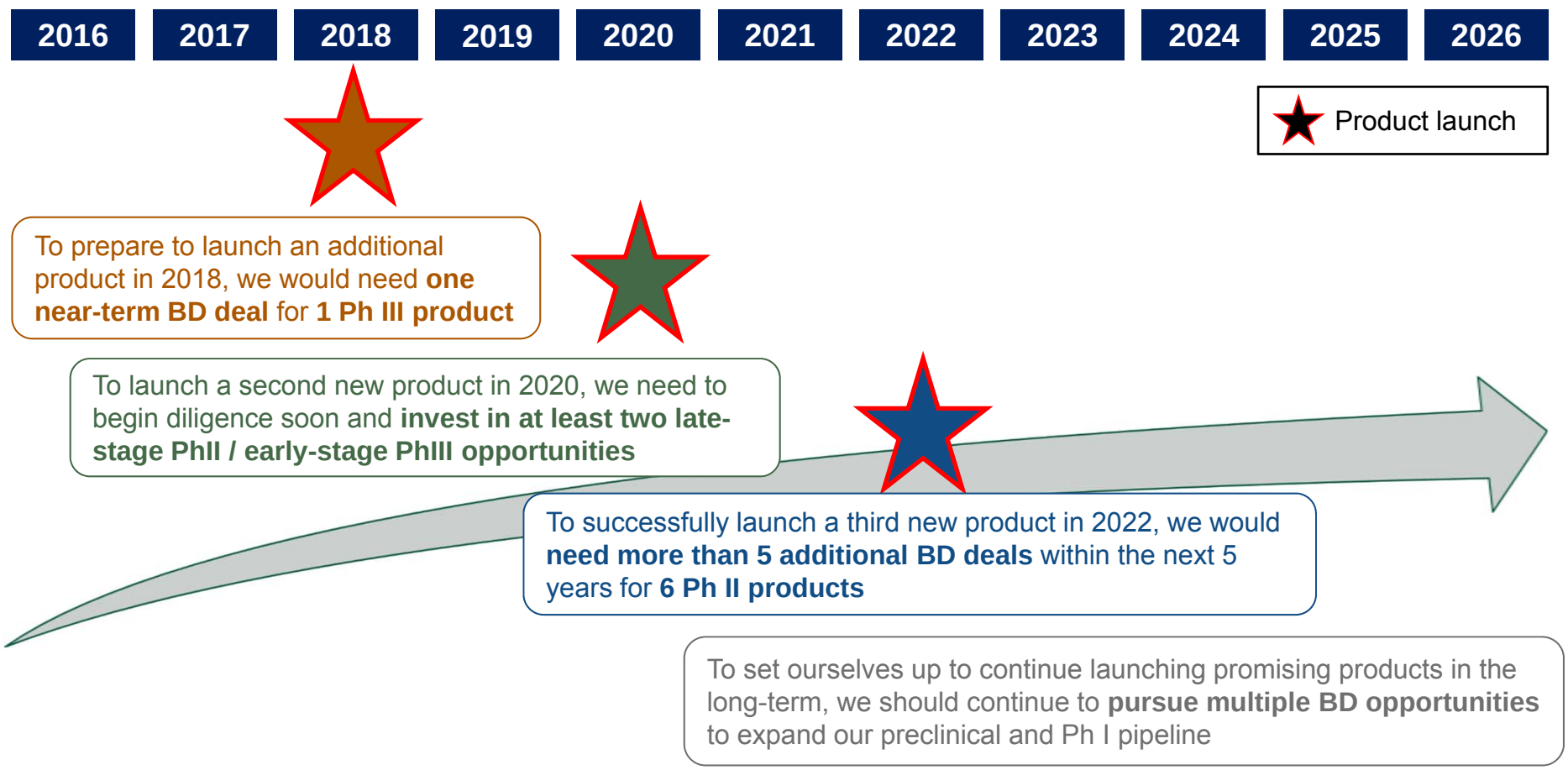
DRAFT

3- BUILD

To continue expanding our pipeline into promising areas in the long-term while filling the pipeline gap, we will and are pursuing a number of BD deals in the near-to-mid term

Positioning of our pipeline and BD assets

INDICATIVE



*We will also continue to **advance our internal pipeline**, in addition to external BD deals*

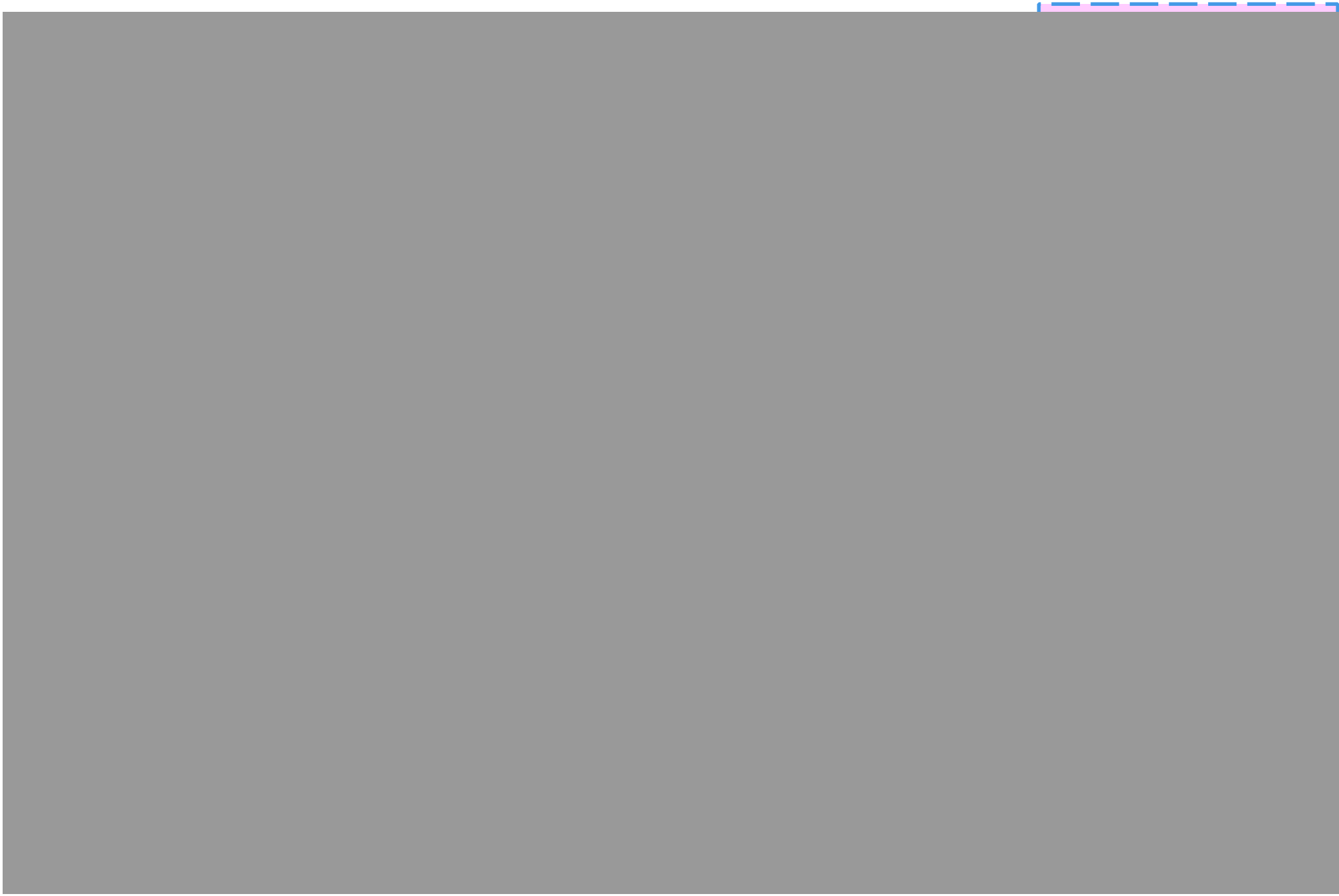
DRAFT

DRAFT

d

Lead region:

DRAFT



DRAFT

We have developed a plan of action to achieve our strategic imperatives

Our strategic imperatives:

1. Optimise our current business
2. Innovate in pain
3. Build a diverse portfolio
4. **Develop the right operational model**

DRAFT

4- RIGHT MODEL

We must develop the right capabilities in order to successfully launch products that meet patient needs globally

1. **Strong commercial strategy capability** at the core of asset selection and development decision making

2. **Robust R&D decision making model** to ensure fast and effective decisions at key development milestones

3. **Enhanced BD capabilities** to ensure early and late stage deals are accomplished through the most effective commercial structure

4. **Cross-functional medical, HE&OR, and regulatory affairs model** to ensure product value is evidenced and communicated

5. **Thinking and aligning globally, but acting and implementing regionally**

DRAFT

1 Strong commercial strategy capability at the core of asset selection and development decision making

- The commercial lead owns the global P&L for the asset and hence plays a key coordinating role in all aspects of the product life cycle
- Deep customer (doctor, patient, payer) insight is critical to first characterising the unmet need, and developing the TPP for a given indication in pain
- Further deep customer insight gathering then will shape the development of the overall strategy
- The commercial lead is responsible for ensuring cross-functional input into the TPP, strategic brand plan and for alignment of the strategic brand plan to the strategic development plan

David/Telea/Graham

Lets align on what we want in here.

We need to talk about what capabilities we have and what we need and then the delta

DRAFT

2 Robust R&D decision making model to ensure fast and effective decisions at key development milestones

Alan/Petra

Please provide detail

We need to talk about what capabilities we have and what we need and then the delta

DRAFT

3 Enhanced BD capabilities to ensure early and late stage deals are accomplished through the most effective commercial structure

Allen/Ann

Please provide detail

We need to talk about what capabilities we have and what we need and then the delta

Our message for potential partners: DRAFT

4- RIGHT MODEL

We are a globally optimised company with regional focus in execution; we have a deep heritage in pain & a commitment to solving the problem of pain

- At Mundipharma & Purdue we are thinking differently about pain. We believe there is still a job to be done for people in pain. We know we can't cure people's pain – but we can give doctors, patients and those caring for patients in pain, the products they need to re-address the pain-life balance.

- We have a proven track record of br ark clinicians and payers early on in pro tive reimbursed, product launches and u anin pain. Over the last three decades w rket Palladone®, MST®, Targin®, Hysin

- Therefore, we uniquely understand t ner treatment decisions - we are workin ds. can aspire to bring something differe

LEK

We need to refine and create versions for different audiences (e.g. for scientific pre-POC partners, for HCPs & KOLs who we want to partner with, for potential collaborators on the commercial side

Ann/Allen

Do we want to add in anything from your corporate deck?

- Our network, with international reach and deep experience in pain has the capabilities to develop, register, manufacture, gain market access and promote pain products all over the world

- We are a virtual company. Our nimble, flexible model enables us to take risks; make quick decisions; and engage with payers and clinicians before we try new ideas. We then pursue these with passion.

- We speak to payers, regulators and clinicians in the early stages of product development. This means we can develop deep insights into what our customers need and can deliver products that will not only get approved but will be welcomed by the market. Only by working together in this way, by sharing ideas and challenging each other, can we make the most out of pain assets.

DRAFT

4 Cross-functional medical, Value Evidence/Access, Safety, and regulatory affairs model to ensure product value is evidenced and communicated

Gail/Harry/Matt, etc

Attached is draft bullets from Gail.
I do see the biggest gap/concern in the value evidence to generate access approach, although I believe colleagues have begun to collaborate

- Asset Specific:
  - Medical Affairs subteams have been established to support each product
  - Lead by individual with knowledge/experience with product
  - Includes representation from all scientific and medical affairs functions and includes global engagement

- Functional: Separately, functional leads meet globally on a regular basis
  - Medical Affairs (eg, external experts, publications, research, disease management)
  - Regulatory
  - Safety
  - Value-evidence/Access
    - Value-Evidence and Access groups have just started to meet but are committed to finding ways to working together efficiently.
    - In US, Purdue has a commercial access group and a medical value evidence group
    - Ex-US, this function, including research aspects, sit entirely within commercial

GDC comment: Medical Affairs will work on a new version of this, notably, we need to add something of what we do, eg, link between health care environment and drug development/

Alix: see new slide next page

Medical Affairs optimizes the healthcare value story across the product lifecycle

Creating EVIDENCE that moves the needle

Clinical Development

- Health outcome measures
- Patient reported outcomes
- Evidence map from trials through to label
- Publication strategy

Commercialization

- Pharmacovigilance
- Regulatory and post-marketing studies
- Medical science liaison engagement plans
- First-rate medical information for customers

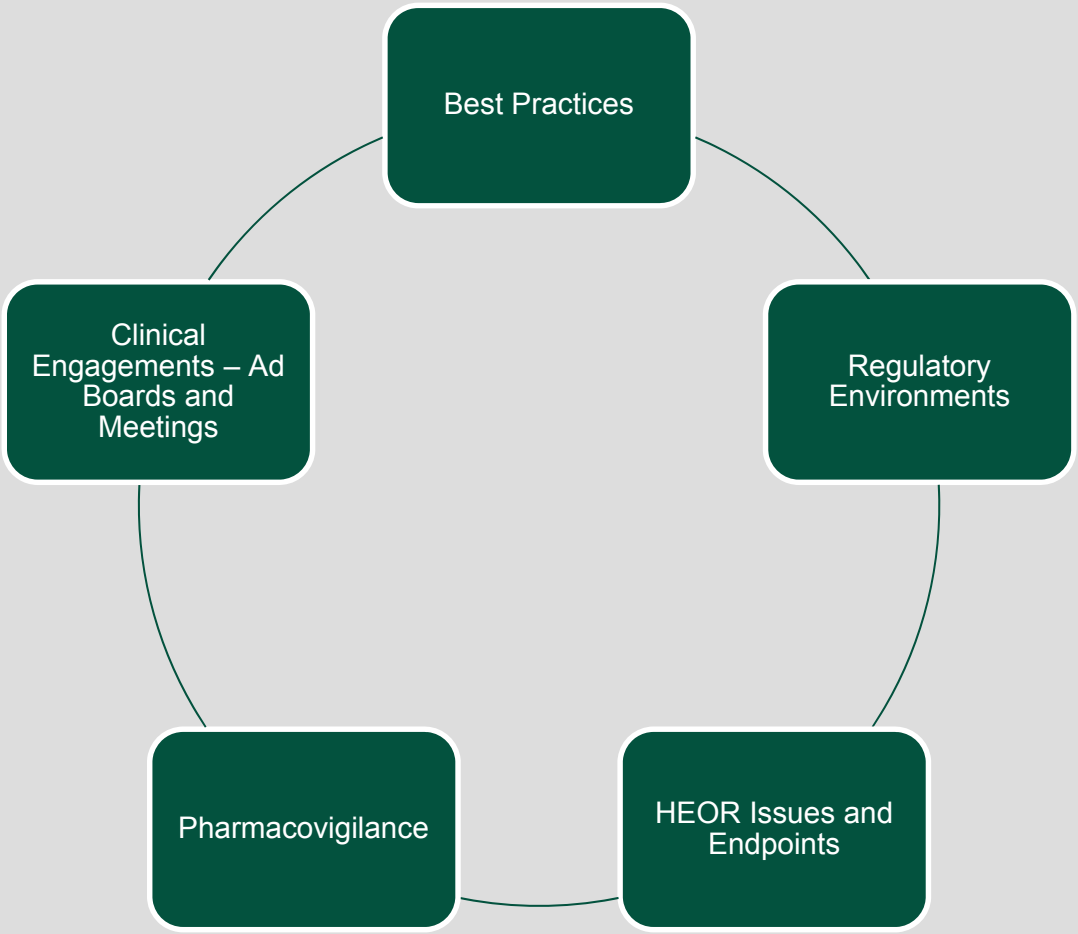
Life-Cycle Management

- Clinical advisor engagement forums
- KOL development
- Uncovering unmet needs to support future product development and positioning

Managed by CROSS-FUNCTIONAL MA teams

Understanding the healthcare environment and the levers that drive adoption

Global Medical Affairs Engagement



Understanding the healthcare environment and the levers that drive adoption

DRAFT

5

Thinking and aligning globally, but acting and implementing regionally: We have set guiding principles to make this work in pain

GPSWG should develop and own the overall pain franchise strategy

Regional strategy should be aligned with the global pain franchise strategy but with regional operational adaptation

Each pipeline asset should be led by one region with global input; this region will be responsible for all global reporting for that asset

We will use the same governance structure for all development assets

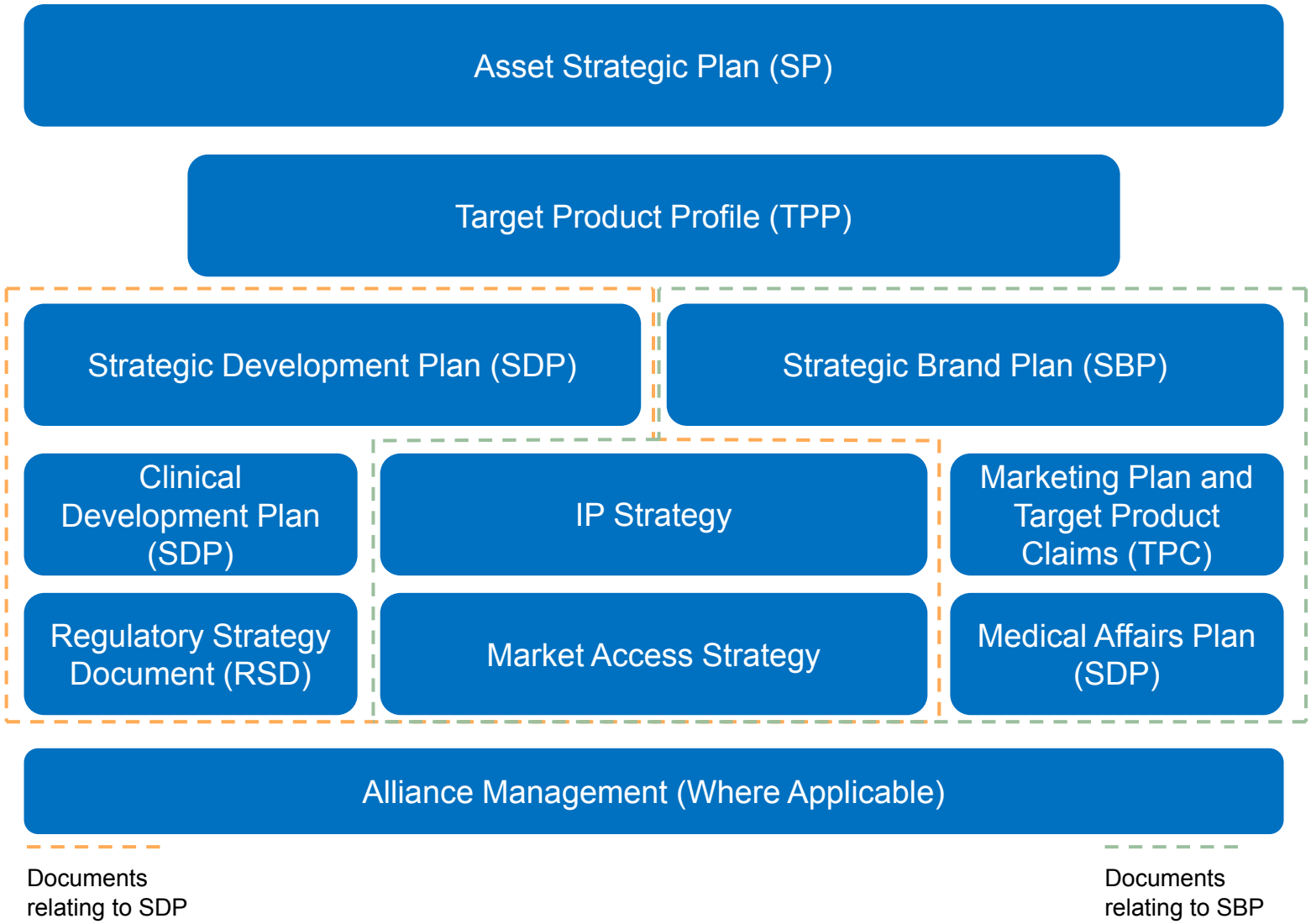
Each asset lead region should be the relationship lead with the partner

Interest in BD assets should be gauged early and input into the DD process collected

A “what COULD you do” attitude is key –
we are already very good at finding reasons why things won’t work…

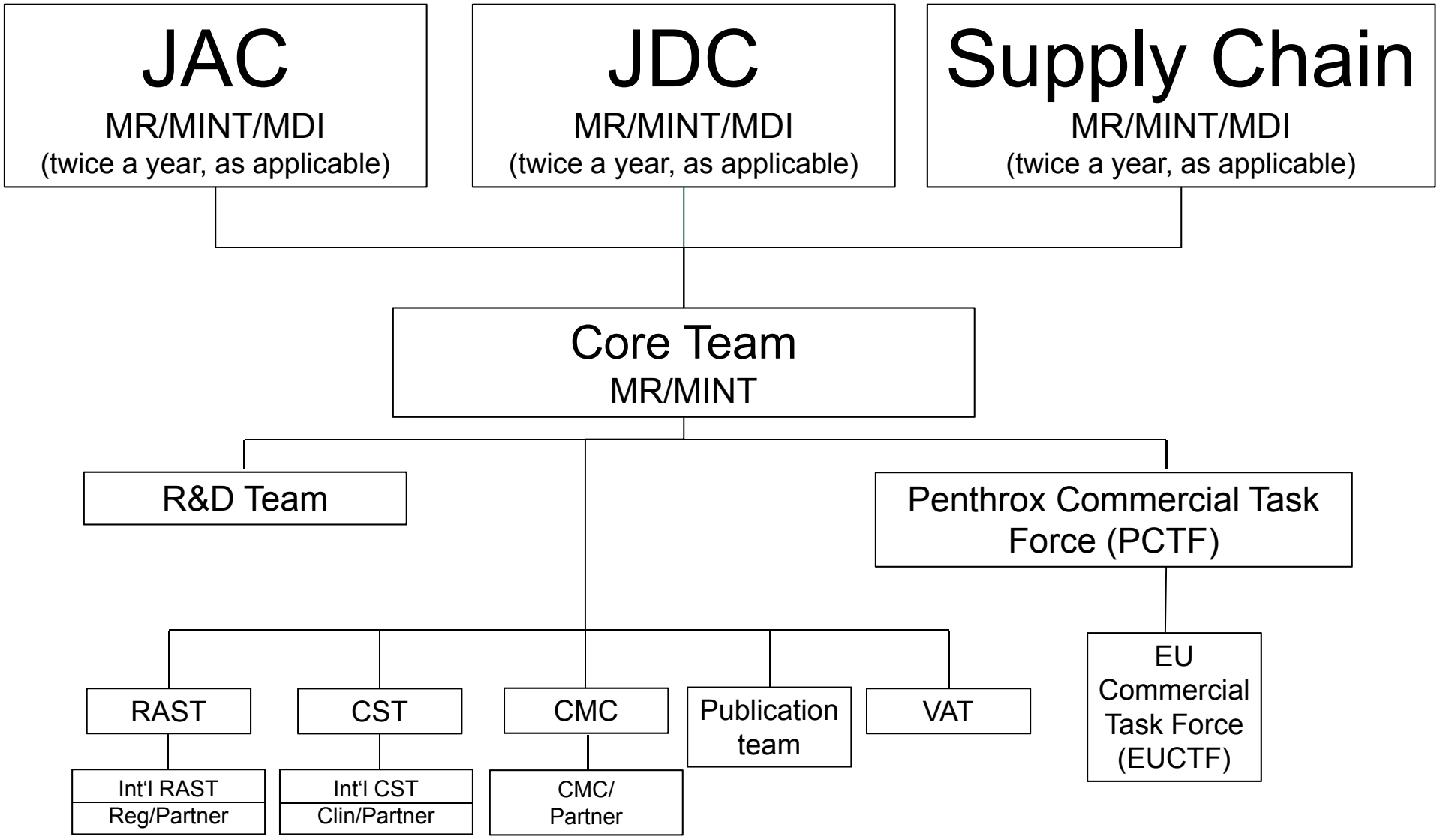
DRAFT

To deliver on the TPP, strategic planning will utilise a wide range of planning documents to facilitate cross functional alignment



DRAFT

Penthrox governance structure



12th April 2016

Sigma global governance

Co-crystal global governance

Petra

Co-crystal global governance

TRKA global governance

Andy/Christian

TRKA global governance

Agenda – today we have covered:

1. **The pain therapy landscape**
2. **Our vision**
3. **Our plan**

Summary

- **Pain remains an attractive market:**
  - The pain market is large, fragmented with significant unmet needs
  - The unmet needs drive the continued search for novel targets to manage pain
  - Our core capabilities in opioids and chronic pain are the ideal springboard to expand into pain
- **Our vision: we can win in pain**
  - We aim to be a global leader in pain, with the unique capabilities & diverse portfolio to establish & sustain a market leadership position
- **Critical to achieving our vision are four strategic imperatives - we must:**
  1. Optimize our current assets
  2. Innovate in pain to lead scientific understanding to identify new targets, measures and treatments
  3. Build a truly diverse portfolio that is driven by customer insights and patient need
  4. Develop the right operational mode

Our pain strategy is ambitious. We must drive a fundamental change in culture throughout the organisation and move from:
product thinking → portfolio thinking;
strong opioid/chronic pain expertise → multiple MoA/broad pain expertise and
local working → global working

Appendix

- Market overview
- Asset progress update
- Benchmarking research
- Indication prioritisation research
- MoA research

Note: Appendix is still in process of revision

WIP – pending feedback from team

The Pain Franchise has evolved significantly in the past year with a focus on moving the pain business forward

	Geographic organisation	Portfolio make-up	Strategic focus	Go-to-market approach
2015	Regional teams making strategic decisions for local markets	Reformulated opioids	Short-term and tactical, confined by opioids	Product-focused decision making
Current	Global communication, with cross-regional coordination on key assets	BD deals to access innovative assets (e.g., Sigma partnership)	Longer-term strategic planning initiated, including MoAs beyond opioids	Progress has been made, e.g. giving pain a voice marketing campaign in MAL
Desired Future	Globally aligned teams with consistent vision across markets; local implementation	NMEs for pain more broadly	Strategic and long term; defined as a pain company, not an opioid company	Portfolio-led decision making

DRAFT

Detailed principles of global working for pain: How to think globally but act regionally

1 GPSWG develops and owns the overall pain franchise strategy

- Each region should support and respect that the pain strategy is owned and developed by the global pain strategy working group

2 Regional strategy should be aligned with global PFS, with regional operational adaptation

- Our global strategy should define our goals, with each region adapting implementation of the global strategy in the context of their regional portfolio

3 Each pipeline asset is to be led by one region

- The global asset lead will "own" the strategy overall
- The global asset lead will be responsible for keeping all regions and functions updated, and collect feedback / information for the asset to input into all reporting requirements (e.g. GPI, board level presentations, et~)

4 The existing governance structure is a starting point for each asset lead

- Each pipeline asset lead should use the existing governance structure as a starting point and vary only where it makes sense

5 A "what could you do" attitude and consideration of optimum effort are encouraged

- Everyone working in pain should encourage their regions to think not why "it will not work" but instead "what could you do" and lead efforts to determine whether or not a given activity / asset is worth the effort required

6 Interest in BD assets is gauged early and input into the DD process is collected

- For business development assets, the lead region should inform the other regions as early as possible to gauge interest and provide input into the diligence process

7 Each asset lead region is the relationship lead with a given partner

- The other regions should respect that each asset lead region is the relationship lead with a given partner, and there should be no back-channelling

Key areas to be highlighted following core team discussion

Global working in pain – Roles and responsibilities

	Responsible per asset → / ↓ *Activity*	GPSWG Core Team	GPSWG Extended Team	RDs	Board	Region R&D	Region Commercial	Region BD	Region Max	Region Medical Affairs	Region Comms
Above -asset	Overall Strategy	A	R	C	I	C	C	C	C	C	C
	Global Pain Messaging	A	C	I	I	C	R	C	C	C	R
	Global Scientific Collaboration	A	C	I	I	R	C	C	I	C	I
	Global Unmet need/ Burden of illness characterization plan	A	C	I	I	C	R	C	C	R	C
	Global KOL Collaboration	A	C	I	I	C	C	I	I	R	I
	International Congress Collaboration	A	C	I	I	C	R	C	C	R	C
	Global Market Access KOL Collaboration	A	C	I	I	I	C	I	R	C	I
	Business Intelligence	A	C	I	I	C	R	C	C	C	I
Asset	Asset strategy, TPP & brand plan	I	I	I	I	C	A/R	I	C	C	C
	Asset development plan	I	I	I	I	A/R	C	I	C	C	C

Key:

R	Responsible	Does the work
A	Accountable	Makes sure the work is done
C	Consulted	Gives input
I	Informed	Informed when it is done

[Placeholder for asset governance maps]

To be received from Petra

Global working in pain – Specific roles and responsibilities

↓ Activity / Responsible per asset →		GPSWG Core Team	GPSWG Extended Team	RDs	Board	Region R&D	Region Commercial	Region BD	Region Max	Region Medical Affairs	Region Comms
Above -asset	Overall Strategy	A	R	C	I	C	C	C	C	C	C
	Global Pain Messaging	A	C	I	I	C	R	C	C	C	R
	Global Scientific Collaboration	A	C			R	C	C	I		
	Global Unmet need/ Burden of illness characterization plan	A	C	I	I	C	R	C	C	R	C
	Global KOL Collaboration	A	C	I	I	C	C		I	R	
	International Congress Collaboration	A	C	I	I	C	R	C	C	R	
	Global Market Access KOL Collaboration	A	C	I	I	I			R		
	Business Intelligence	A	C	I	I	C	R	C	C	C	I
Asset	Asset strategy, TPP & brand plan	I	I	I	I	C	A/R			C	C
	Asset development plan	I	I	I	I	A/R	C			C	C

Kate H/ David X

Kate H

Allen D/ Karen R

Harry/ Gail

Kate H

Harry/ Gail

Kate H

Harry

Kate H/ David X

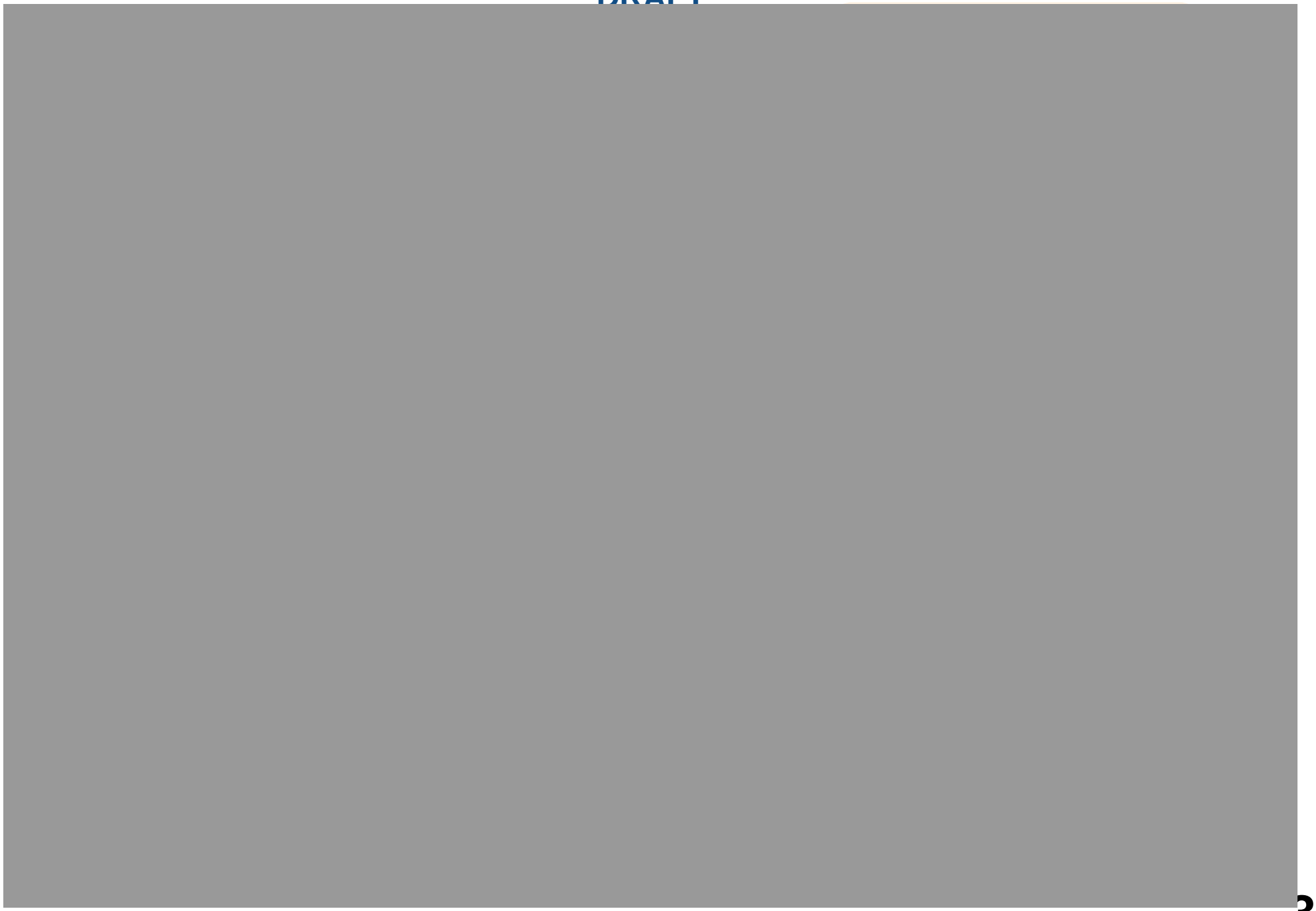
Matt H/Stella K

See next slide

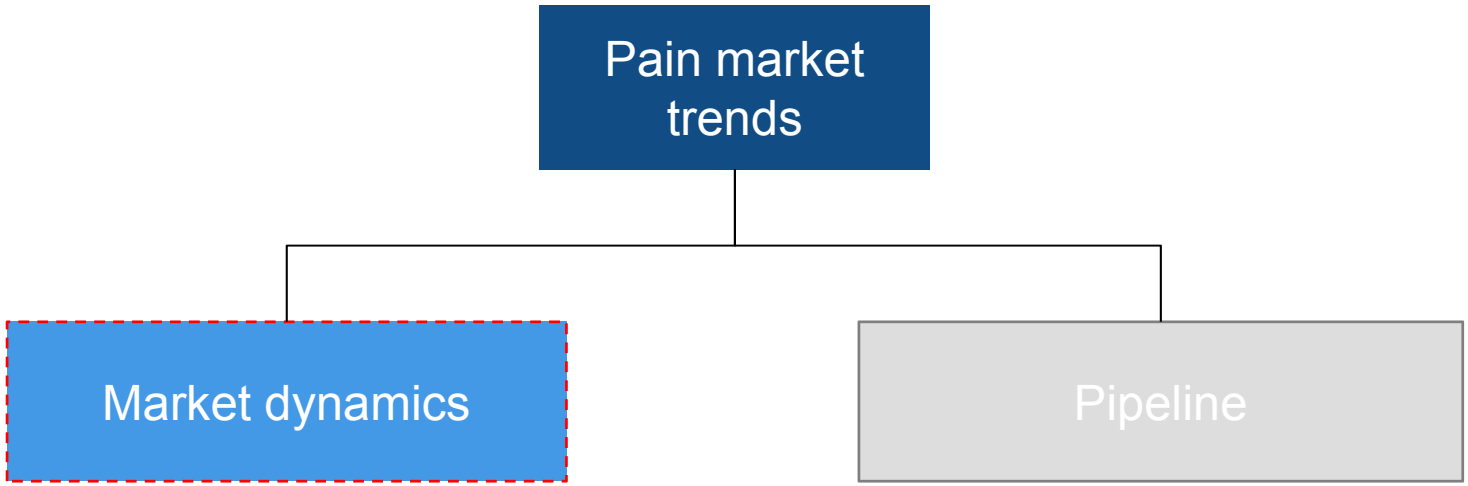
Key:

R	Responsible	Does the work
A	Accountable	Makes sure the work is done
C	Consulted	Gives input
I	Informed	Informed when it is done

Lead

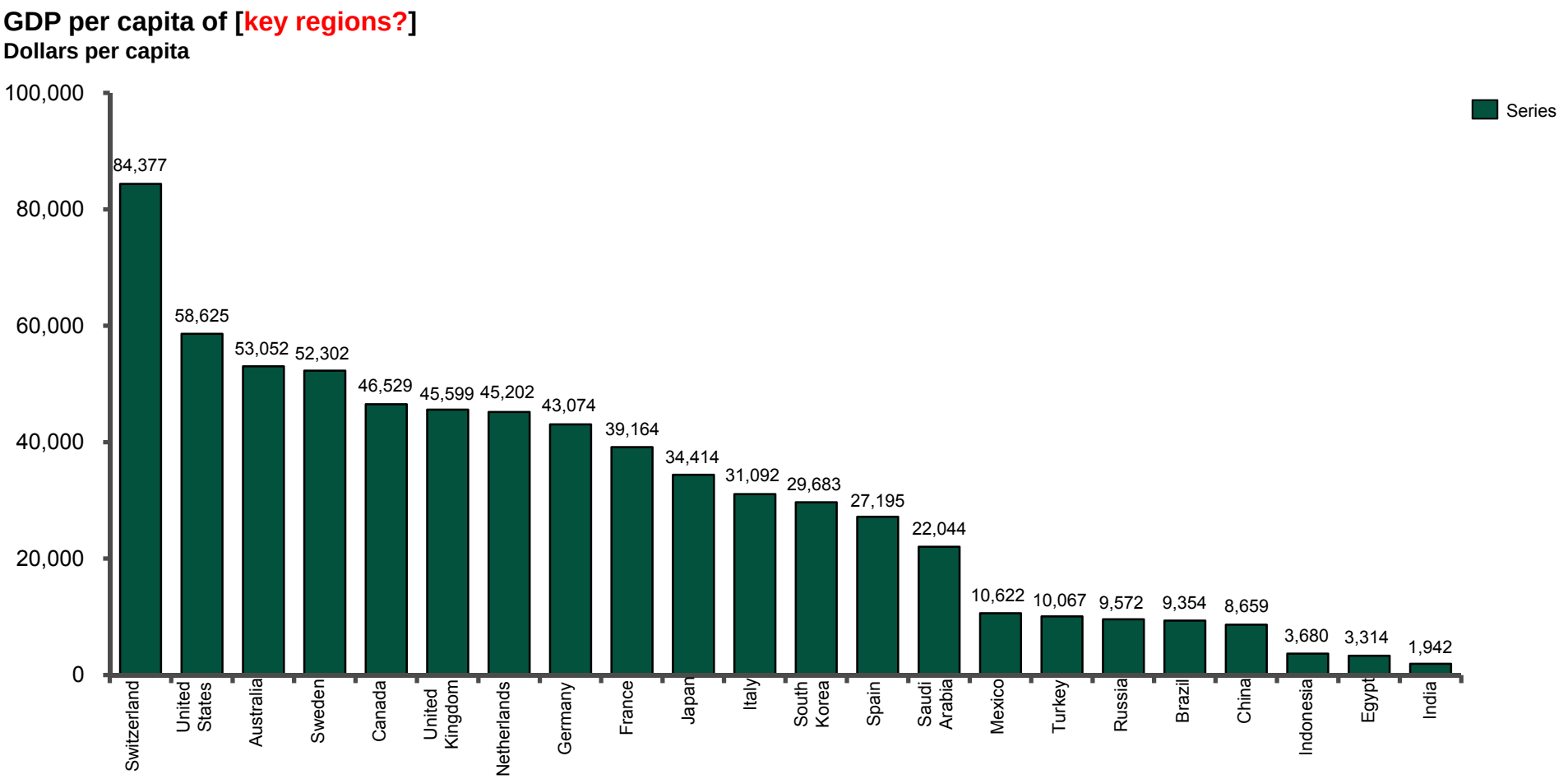


A number of trends in the pain market will shape our strategy



DRAFT

Australia, Canada, the U.S. and the EU5, which account for >50% of the value of the pain market, have GDP per capita over $20,000

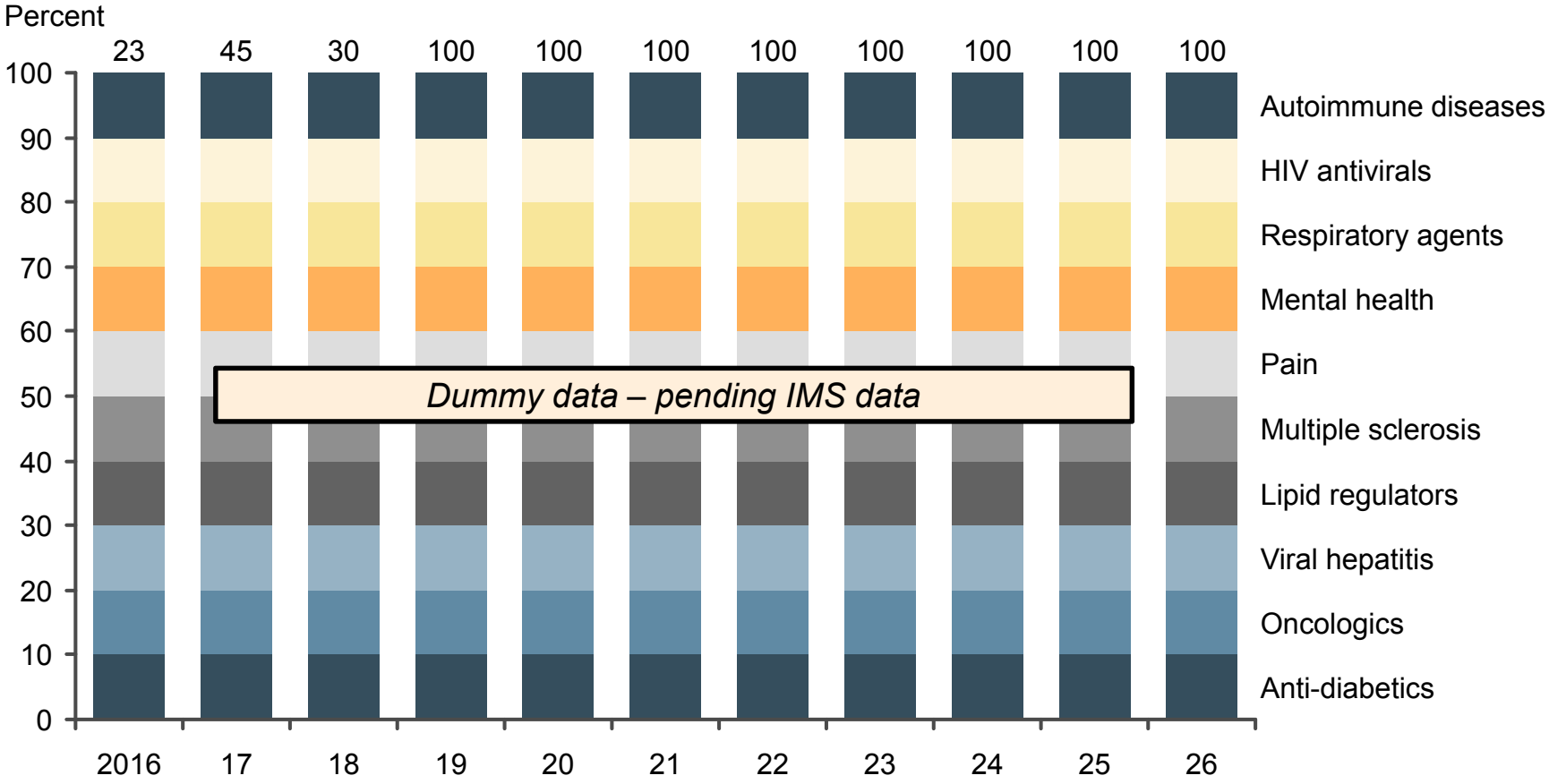


Source:

Tag is WIP depending on IMS data

Pain is set to continue to be the largest Rx pharmaceutical market by value, representing x% of the total global market

Proportion of global pharmaceutical volume by therapeutic area (2016-26)



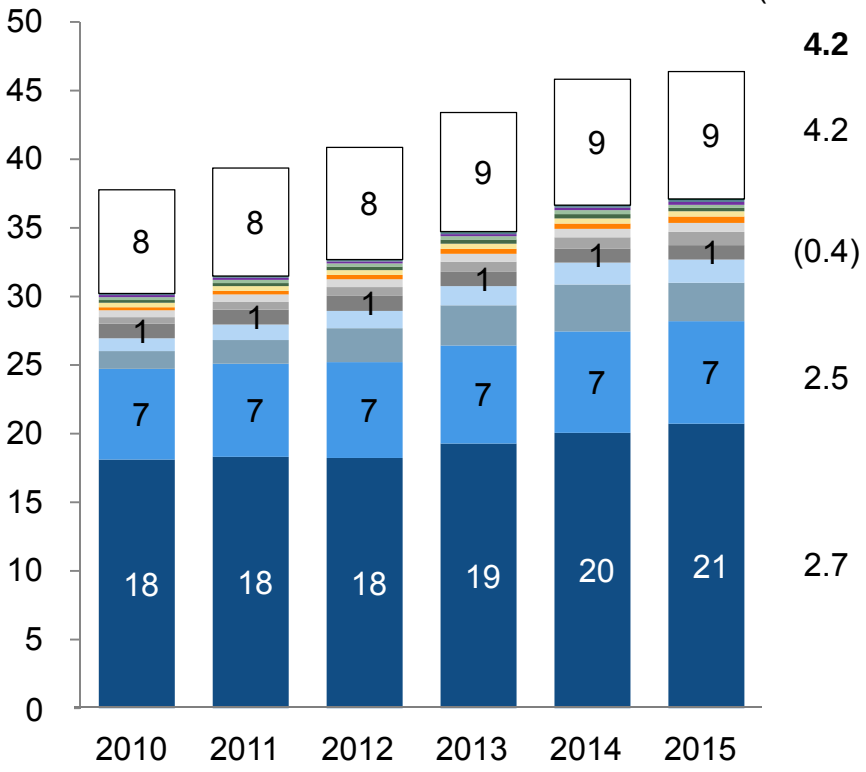
Note: CAGR % is for 2010-2014
Source: IMS MIDAS MAT Q4 2014; IMS MEDICAL MAT Q4 2014

DRAFT

Developed markets continue to represent the larger share of both the value and volume of sales in the pain market, although emerging markets are growing faster

Global pain market value (2010-15)

Billions of dollars



CAGR (2010-15)

4.2

4.2

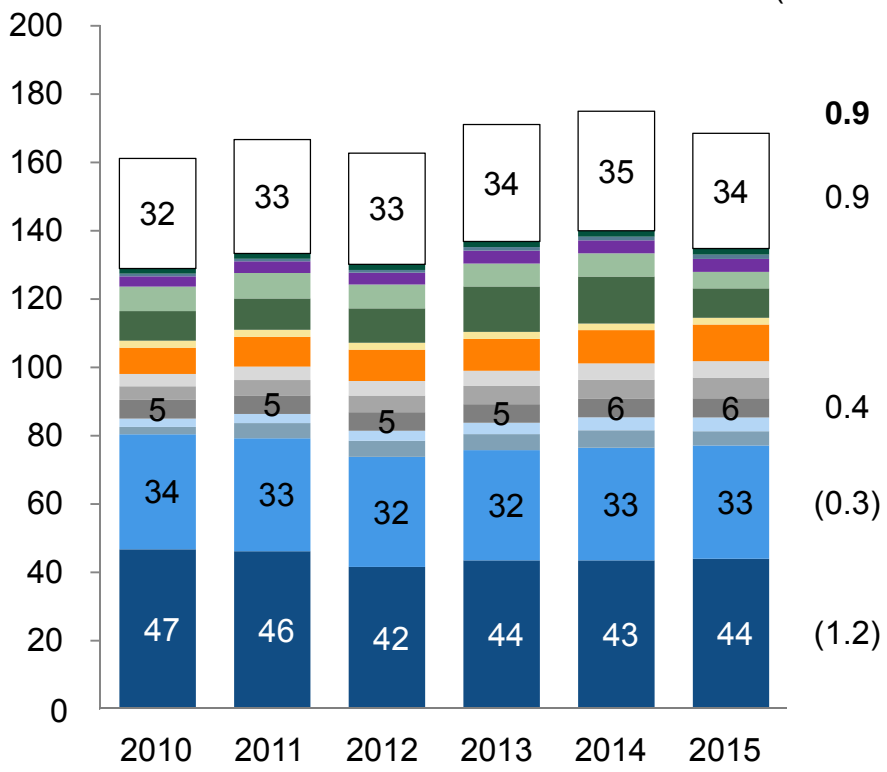
(0.4)

2.5

2.7

Global pain market volume (2010-15)

Billions of standard units



CAGR (2010-15)

0.9

0.9

0.4

(0.3)

(1.2)

USA, EU5, Canada, Japan, Australia, India, Indonesia, Russia, China, Brazil, Mexico, Turkey, Egypt, Saudi Arabia, RoW

Note: Geographies include - Developed: EU5, USA, Australia, Canada, Japan, Emerging: Brazil, Russia, India, China, Mexico, Indonesia, Egypt, Turkey, Saudi Arabia (ROW, scaled up to 1.25)

Source: IMS MIDAS sales MAT Dec 2015

DRAFT

[Payers continue to grow in importance. Translating clinical benefit into value is critical to long term success]

To be updated by Mundi/Purdue market access team

Story:

- Payors continue to grow in importance
- Translating clinical benefit into value, as perceived by payors, is critical to long-term success
- Implications:
  - Evidence
  - Way we design clinical trials
  - Showing benefit in different patient populations
  - Next level: here's how you do that

DRAFT

[Other tactics that will define how we implement our strategy]

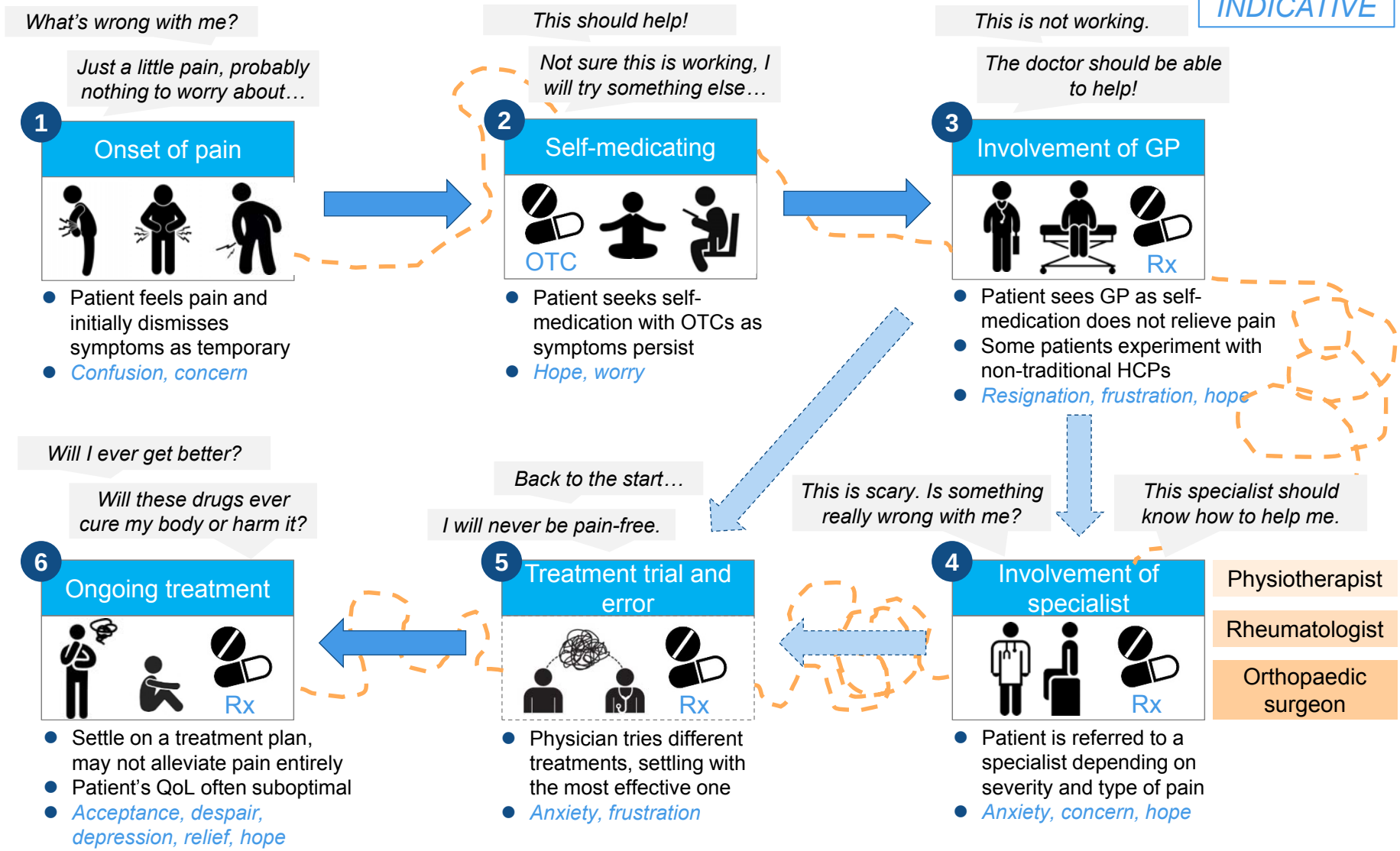
Healthcare dynamics	Tactical implications
Increasing role of digital health for providers and patients	• Increasing technification of healthcare may require a digital strategy in order to create a holistic value proposition in pain • Need to digitally engage with physicians to market products • Opportunity to encourage patients to seek and comply with treatment while tracking and analysing patient / trial data
Changing nature of **patient engagement** with physicians and pain treatment	• Opportunity for new tactics, including broader and earlier stakeholder interaction, to engage with patients and encourage treatment • Increase in co-pays and private pay could impact patient treatment preferences
Expansion of **universal healthcare** into an increasing number of markets	• Opportunity to continue launching and growing products in new markets • Need to consider implications of government-funded healthcare and budgetary pressure on pricing, reimbursement and product access

DRAFT

Pain remains a confusing journey for both patients and physicians alike

Overview of the pain patient journey

INDICATIVE



Source: Management

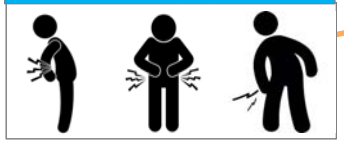
DRAFT

There are a number of unmet needs that need to be addressed to improve the pain patient journey experience for both patients and physicians

Needs | Opportunities

Key needs for the pain patient journey:
- Improve patient experience (*emotional counselling*)
- Reduce HCP frustration with pain treatment (*education on diagnosis, treatment options*)
- Use effective pain treatment options with minimal side effects and low chance of abuse

1 Onset of pain



- Patients to learn to recognize ***early signs*** of pain
- Patient education about pain and its implications, e.g. through dedicated website sources
- Apps to help patients ***track symptoms***

2 Self-medicating

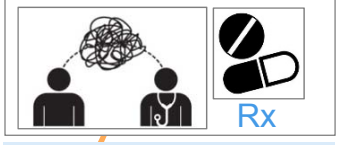
- Patients to learn to ***go to physician early*** and get diagnosed, especially for some types of chronic pain
- Patient ***education*** about pain and its implications
- Apps to help patients ***track treatment and symptoms***

3 Involvement of GP / specialist

4

- Physicians to better ***diagnose*** pain
- Physicians to ***motivate*** patients to be responsible and return to functioning lifestyle
- Increase patient ***access*** to the right specialist
- Physician ***education*** on how to better ***manage*** pain
- Patient ***education*** on what pain ***diagnosis*** means
- Patient ***support with emotional burden***

5 Treatment trial and error



- Where possible, ***move away from opioid use***
- Patients and physicians to be encouraged to ***use ADF*** to mitigate abuse
- Help patients and physicians ***choose the best treatment***
- Patient ***support with emotional burden***

6 Ongoing treatment

- Patients to learn how to ***best manage their treatment*** and reduce emotional burden
- Patients to learn how to ***prevent abuse*** where applicable
- ***Compliance and treatment*** tracking
- Patient ***support with emotional burden***

Key opportunities to address unmet needs:
- Provide greater support to the burden placed on both patients and physicians when it comes to understanding and treating pain
- Help build a better understanding of pain conditions and their treatment
- Provide effective pain treatment options in addition to opioids

Source: Management

DRAFT

The current practices and perceptions of pain management in Asia present both an opportunity and a challenge

Based on ACHEON survey of physicians and patients in Asian countries

State of pain management in Asia

- Pain is frequently under-treated in Asia, where there are a number of barriers to optimal pain management
  - inadequate physician training and awareness leading to inadequate assessment of pain
  - excessive regulations and low opioid access
  - low referral rates to pain management centres or lack of such services
  - patient misconceptions regarding pain alleviation
  - cultural taboos discouraging outspokenness about pain
  - patient (and sometimes physician) perceptions about opioid use, e.g. side effects, addiction

Opportunities to improve pain management in Asia

- Help provide physician education to improve pain assessment practices and bolster confidence in prescribing complex therapies
  - for example, become involved in continuing medical education
- Help increase patient awareness through counselling and education on pain treatment and opioid use
  - help reduce cultural taboo of chronic pain treatment overall
  - address the opioid stigma to improve current standards of patient care
- Help increase access to opioid medications by not just providing these medications but also bolstering referrals to the right prescribers

Mundipharma MAL have already launched a digital platform aiming to tackle some of these needs

Source: ACHEON studies (Kim *et al*., 2015, Cancer Medicine and Cheung *et al*., 2016, Pain and Relief)

DRAFT

In order to enable successful expansion and growth, we have designed a plan of near-term and mid-term tactics

2016

Protect opioid business

- ❑ Evaluate ADF opportunities that can protect our core
- ❑ Opportunistically pursue acquisitions, e.g. Portland
- ❑ Continue to advance our pipeline
- ❑ Continue to transform global working practices and SOPs to capitalise on synergies

2016-20

Expand and progress a diversified pipeline

- ❑ Form connections with leading KOLs and academic centres to remain at the forefront of science in pain, encompassing opioid and non opioid therapeutics
- ❑ Assess scientific evidence in support of MoAs via virtual discovery organisation
- ❑ Continue to pursue innovative BD opportunities, following our Sigma, TRKA and Nav1.7 deals, positioning ourselves as the pain-focused partner of choice
- ❑ Leverage ‘opioid 2.0’ to strengthen opioid franchise and build presence in global growth markets

2020-26

Broad portfolio of opioid and non-opioid pain management

- ❑ Consider strategies to optimise the patient journey beyond simply pharmaceuticals
- ❑ Establish position as the broad leader in pain therapy across pain conditions and agnostic to MoA through
  - ❑ deep KOL relationships
  - ❑ broad clinical develop programmes
  - ❑ global awareness and education programmes

DRAFT

To achieve our 2026 vision, alongside strategic steps we should pursue tactical changes in interactions with key stakeholders

FOR CORE TEAM DISCUSSION

2026 vision

Broad leadership in pain, across MoAs and indications

Strategic steps

- Optimise opioid core
- Expand & diversify portfolio
- Cement positioning as global pain leader

Tactical requirements

Patients

- Engage patients along the entire pain journey, regardless of treatment and condition
- Leveraging digital tools that help patients engage with opioid treatment and management throughout the patient journey
- Establish ourselves as the go-to resource for patients for all pain related information, through multiple channels

Physicians

- Messaging and narrative to physicians around our position in pain, not just in opioids
- Leveraging digital tools that help physicians access information on their own terms
- Establish ourselves as the go-to resource for physicians for all pain related information, through multiple channels

Payors

- Innovate with payors on pricing and market access
- Early dialogue with payors on product launches and value potential of diversified portfolio
- Look for innovative portfolio/outcomes-based pricing and access opportunities

DRAFT

To optimise the opioid core, Mundi/Purdue should address key challenges across stakeholder groups through a mix of communications channels

Stakeholder group	*Key challenges*	*Tactical opportunities*
Patients	• Confusion around pain- more information sources, more channels • Increasing media coverage on opioid phobia • Lack of acknowledgement/treatment in emerging markets • Increasing co-pays • Frustration at poor long-term outcomes in pain	• Digital tools e.g. apps that engage patients in their opioid treatment, for their condition at their specific point on the patient journey • Address opioid stigma and educate patients on appropriate use and safety • Provide tools to help patients navigate physician relationships • Explore innovative access opportunities
Physicians	• Changing patient relationships • New ways and channels to access information • Increasing uncertainty around the appropriate use of opioids • Low willingness to prescribe in emerging markets	• Continuing education on appropriate management of chronic pain with opioids • Intergrating digital tools to communicate product messages/education on their terms- enable access to relevant information at relevant points in time • Work with KOLs to create consensus on opioid usage
Payors / regulators	• Changes in regulations in opioid usage and reimbursement • Budgetary pressures on pricing • Percieved ineffectiveness of ADF technologies	• Engage in early dialogue with payors on pricing issues, particularly relating to patent expriries • Look for HEOR impact of opioids and identify opportunities to communicate budget and patient impact of ADF technologies
Company	• Patent expiry of core products • Some markets yet to launch key products • Shift from regional to global pain teams, new SOPs in place for global working	• Potential to switch treatments (if BD/launch opportunities to do so exist) • Work with governments/regulators in key markets to ensure successful access to core products in emerging markets • Communicate internally the need to optimise opioid business

DRAFT

To support portfolio expansion, Mundi/Purdue should communicate and tactically leverage the new value proposition of our broad portfolio across stakeholders

Stakeholder group	*Key challenges*	*Tactical opportunities*
Patients	• Confusion around pain- more information sources, more channels • Lack of engagement and knowledge around pain treatments • Frustration at poor long term outcomes	• Digital tools e.g. wearables/apps that engage patients in the journey they are on, helping them to engage in holistic treatment, manage symptoms and their own data • Provide tools to help patients navigate physician relationships • Explore innovative access opportunities
Physicians	• Changing patient relationships • New ways and channels to access information • Lack of treatment options • Perception of Mundi/Purdue as an 'opioid company'	• Education on holistic pain management, MoAs and their potential usage across indications • Digital tools to communicate new trial data and treatment options • Changing messaging/narrative around Mundi/Purdue in pain
Payors / regulators	• Unknown perceptions of new MoAs in pain • Unknown willingness to pay in highly genericised market • Considerable efficacy/safety differentiation required in most conditions for premium pricing and access	• Engage in early dialogue with payors on new product launches-understand product value drivers and optimal product positioning
Company	• Large change in pain portfolio narrative- away from chronic/acute and opioids to indication focused and holistic	• Internal communication and engagement on change journey • Education on new ways of seeing pain and company strategy

DRAFT

To establish broad leadership, Mundi/Purdue should invest in tactics that demonstrate commitment to optimally treating pain along the pain journey

Stakeholder group	*Key challenges*	*Tactical opportunities*
Patients	• Frustration at poor long term outcomes	• Establish Mundi/Purdue as the global authority on pain, providing detailed information and resources for patients online and offline to enable them to achieve better outcomes
Physicians	• Frustration with treatment options and lack of clarity around best practice • Perception of Mundi/Purdue as an 'opioid company'	• Establish Mundi/Purdue as the global authority on pain management, providing physicians with multi-channel resources on treating pain and painful conditions • Potentially sponsor long term clinical/observational studies on pain treatment and management across conditions to advance global knowledge and best practice
Payors / regulators	• Considerable efficacy/safety differentiation required in most conditions for premium pricing and access	• Potentially look at innovative portfolio based pricing strategies • Potentially look at pricing strategies based on treatment outcomes
Company	• Large change in pain portfolio narrative- away from chronic/acute and opioids to indication focused and holistic	• Internal communication and engagement on change journey • Education on new ways of seeing pain and pain strategy

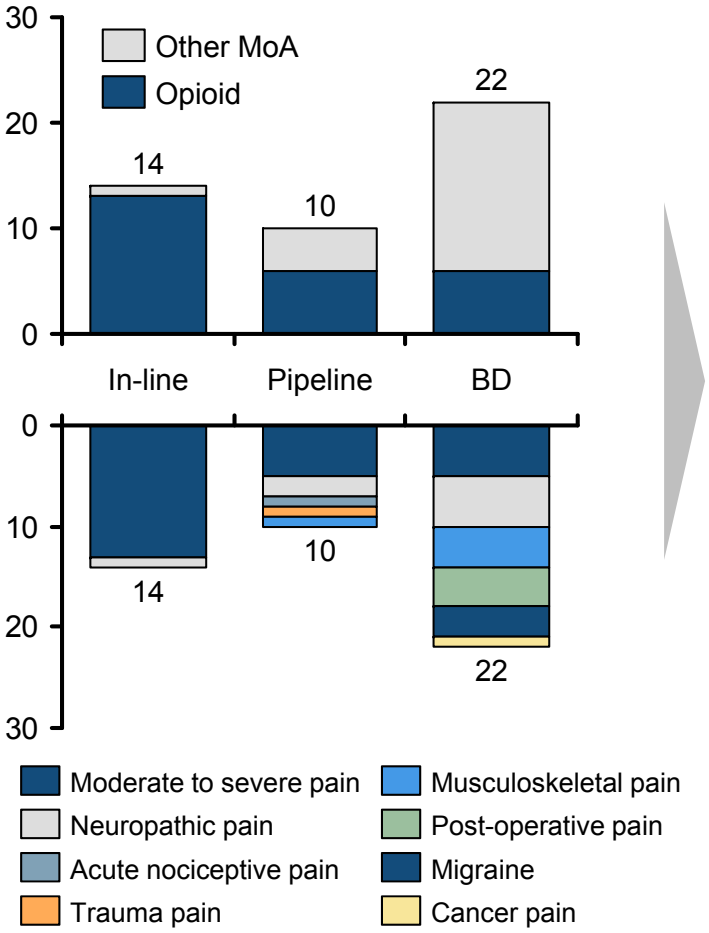
DRAFT

To improve the patient journey while meeting previously-unrecognised unmet needs for patients, we may consider opportunities beyond pain medications

FOR DISCUSSION

MDP / Purdue in-line, pipeline and BD assets* (March 2016)

Number of assets



Management of opioid stigma

- Opioids are likely to remain a key component of MDP / Purdue's portfolio
- MDP / Purdue should continue to address the opioid stigma, especially in some geographies, to improve the standards of patient care

Disease management beyond opioids

- MDP / Purdue's pipeline and BD assets reflect a willingness to move away from opioids to novel SoCs in pain management
- Adapting to market sentiments and disease management needs at the portfolio level should remain a key imperative for MDP / Purdue

Assets that target specific diseases

- Having assets with more specific indications will give MDP / Purdue the option to participate in the patient journey associated with them
- Disease management on an asset-by-asset level could give MDP / Purdue an advantage from both physician and a patient perspective

Provide a holistic treatment for patients

- To become "the" pain management company, MDP / Purdue should aim to provide a holistic approach to pain treatment
- In addition to supporting the patient through the emotional journey with education, digital solutions and others, expansion into ancillary areas, such as depression / anxiety could be considered

Note: * Only pipeline assets for which information has been provided by management have been included. Only BD assets for which are in assessment have been included.
Source: Management

DRAFT

Technology is increasingly incorporated into healthcare via digital health, which can offer several benefits to the pharmaceutical industry

Apps and software solutions

Description

- Applications that enable the patient to self-manage pain, monitor progress, receive peer support, et~
- Software solutions that enable telemedicine: patient care over distance with healthcare professional involvement

Benefits to pharma

- Engage patients in their own care
- Improve overall patient care, experience, and compliance
- Optimise disease management and patient care in the shift to value-based care

Wearable technologies

Description

- Wearable devices that can be used by patients either to provide pain relief or to monitor a pain management therapy

Benefits to pharma

- Potential to augment a drug therapy
- Improve overall patient care and experience
- Potential to access / collect patient data

Use of technologies in clinical trials

Description

- Software solutions that may or may not involve use of wearable devices / apps that enable data collection during clinical trials

Benefits to pharma

- More efficient clinical trial data collection
- More reliable and reproducible clinical trial data
- Better clinical trial data storage

Use of big data to monitor drug use and side effects

Description

- Data collected from online sources, such as biomedical literature and social media / forums, which can be used to understand patient behaviour

Benefits to pharma

- Monitoring of drug use
- Early detection of potentially harmful drug effects, e.g. DDI

Digital health solutions have the potential to enhance patient experience, improve clinical outcomes and reduce the cost of healthcare, presenting a potentially attractive opportunity for the pharma industry

DRAFT

Novel digital health technologies are likely to be increasingly used in pain management at the patient, healthcare provider and industry levels

Apps and software solutions: high use in pain

- There are hundreds of **patient-focused apps** aiming to manage chronic pain and improve quality of life
- Most are simple and do not involve healthcare professionals but have not been tested for pain-related outcomes
- There is a need to develop apps that provide the theoretically- and empirically-supported strategies provided by face-to-face self-management programmes
- Apps and other software are likely to be increasingly employed to enable consultations and patient monitoring with the involvement of healthcare professionals and providers (**telemedicine**)

Examples

Wearable technologies: moderate use in pain

- Some **wearable technologies** that block pain-related nerve signals and provide pain relief have been developed
  - e.g. Quell (a leg band) has been approved by the FDA; CUR (a patch) is awaiting 510(k) clearance
- Intelligent wearables are likely to be increasingly used to track pain management and adapt recommendations to each patient

Examples

CUR

Quell

Use of technologies in clinical trials: limited use in pain

- **Electronic patient reported outcomes (ePROs)** are likely to be more and more used in clinical trials to improve the reliability, reproducibility and storage of trial data

Examples

CRF HEALTH ERT Getting It Done. Right.

Use of big data to monitor drug use and side effects: limited use in pain

- Use of **big data** mined from biomedical literature sites, social media, dedicated forums and other online sources to learn about drug use, potentially dangerous drug side effects and interactions, et~ could develop in the pain space
- The usefulness of scanning biomedical literature for potentially dangerous drug-drug and of Twitter mining in the surveillance of infection outbreaks have already been demonstrated in research publications

Level of use in pain: High | Moderate | Limited

Source: Hamed et al. (2015) Journal of Biomedical Informatics; Lalloo et al. (2014) The Clinical Journal of Pain livescience.com; paindoctor.com;

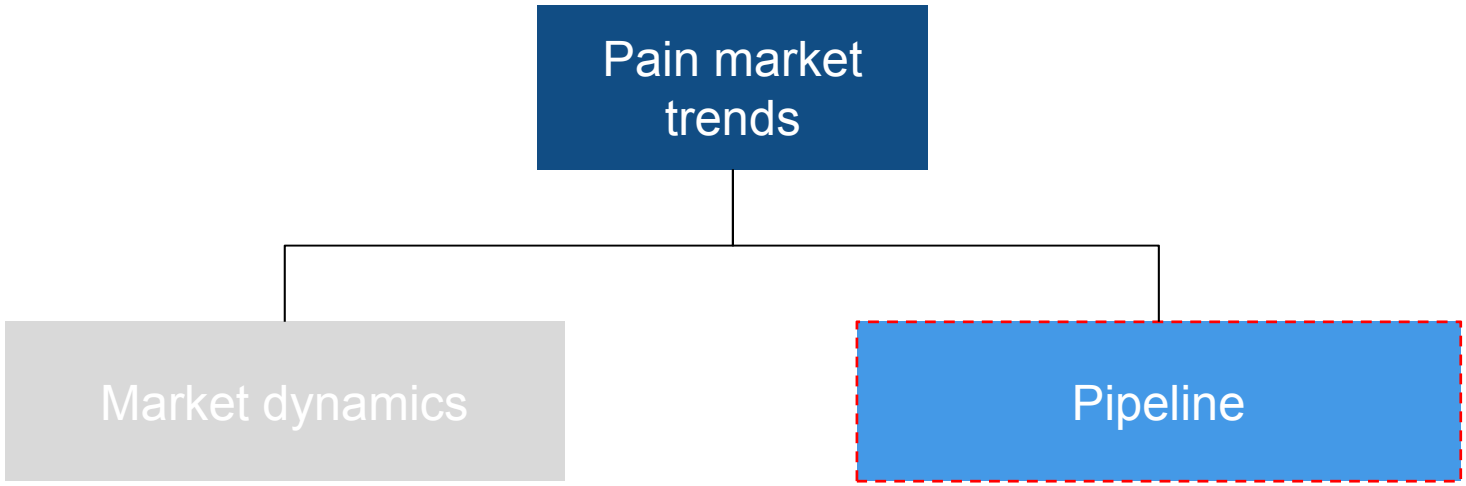
DRAFT

Regional stance on opioid abuse has remained largely unmoved since 2015, with the FDA final guidance on production of abuse-deterrent opioids the most recent change

			
Countries			
Prevalence of inappropriate opioid use	Inappropriate use of prescription drugs exists, but is poorly characterised and not to the same scale as in the US	Diversion and tampering are frequent in the US as prescription opiates are easily available to patients	Inappropriate use of opioids is uncommon
Consumer demand for opioids	Absence of direct-to-consumer marketing of opioids in Europe limits patients' demand	US consumption of opioids is more than 2 times that of many EU5 geographies, per capita, driven by private patients	Lack of demand and widespread awareness of opioids; patients wary of products not aimed at treating underlying conditions
Access to opioids	Robust systems of prescription registration are in place in EU5 countries, that more strictly regulate opioid prescription than in the US	Easy access to medications is considered the key reason for a higher abuse / misuse prevalence than in the EU5	Opioids difficult to access; low physician willingness to prescribe prevents a widespread problem
Importance of abuse deterrence	**No planned additional steps towards limitation of abuse – relatively strict prescribing regulations are already in place in the majority of the EU**	**Perceived "epidemic" of abuse in the US continues to drive FDA guidance around the production of abuse-mitigating opioids**	**More important to improve awareness and educate on opioids as an effective medication in the right environment**

April 1, 2015: FDA releases final guidance for developing abuse-deterrent opioids

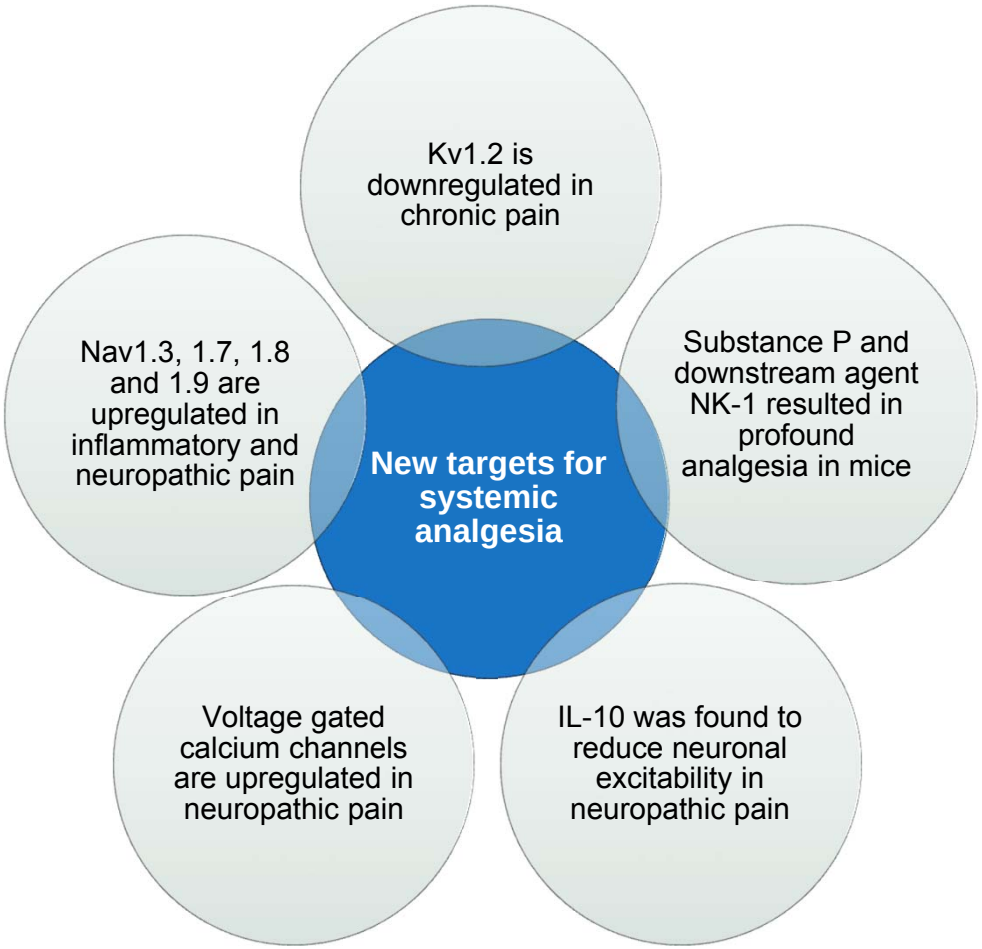
A number of trends in the pain market will shape our strategy

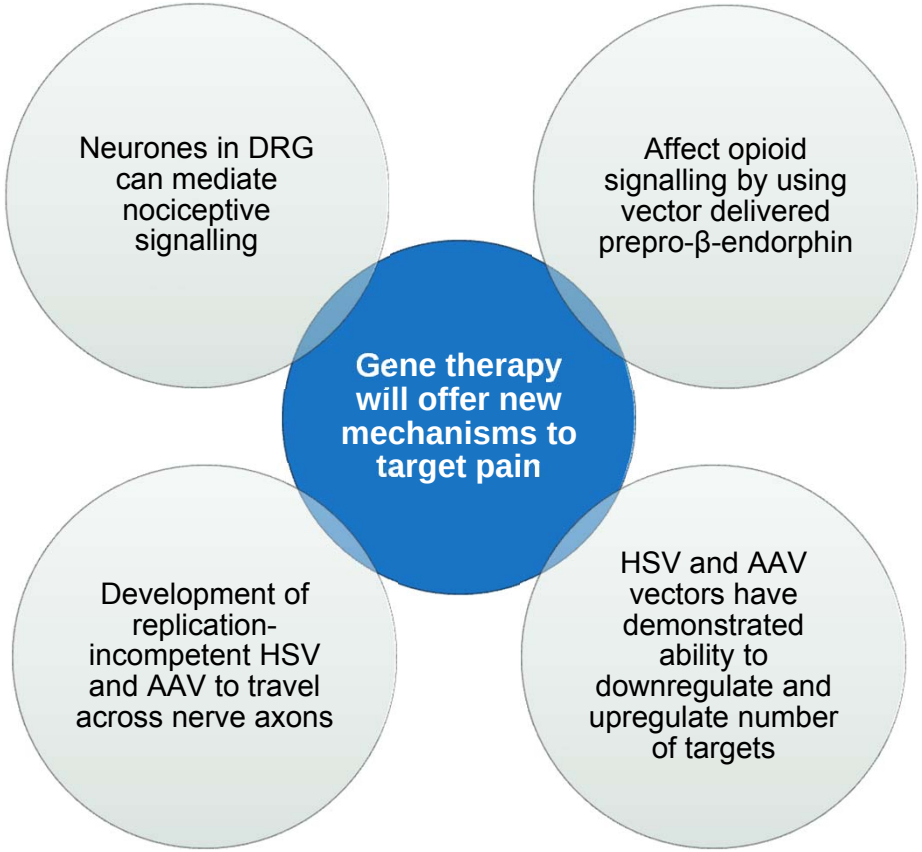


DRAFT

The science of pain is advancing, as we now know more about the molecules involved in pain signalling and are learning about their regulation through gene expression

NOT EXHAUSTIVE





Although we have made significant steps forward in identifying biomarkers which objectively record pain, either through the measurement of inflammatory markers or functional MRIs, further research is needed to improve sensitivity and specificity of such tests

Note: Other advancements include larger application of conventional drug discovery paradigms through phenotype-directed screening and target-directed screening thanks to the improved understanding of the mechanics, better understanding of the opioid signaling of the NOP, MOP and KOP receptors

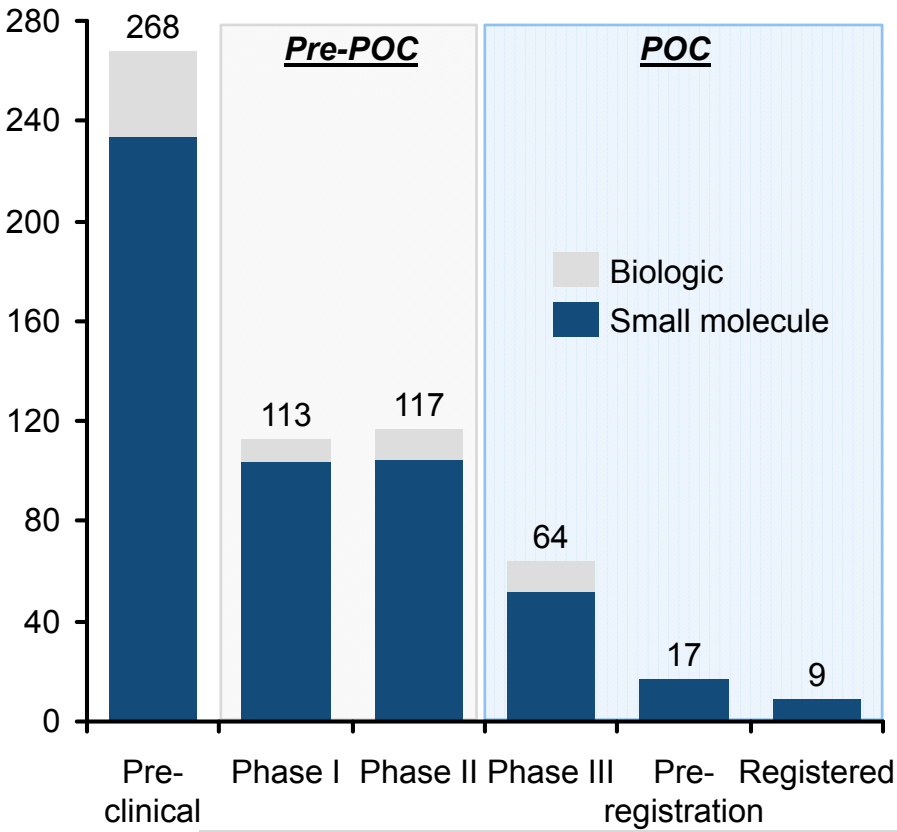
Source: Mayo Clinic, Symposium on Pain Medicine, 2016

DRAFT

590 assets are in development for pain, with 65% of these assets in early stages of development

Number of unique assets in development for pain* (February 2016)

Number of assets



	Pre clinical	Pre-POC	POC
Biologic	34	21	12
Small molecule	234	209	78

- A total of 590 unique assets are in development for pain-related indications
  - 65% of all unique assets in development for pain management are early, i.e. pre-clinical and Phase I, assets
  - 20% of these assets are novel opioid MoAs or new formulations of old opioid MoAs
- The majority (90%) of assets are small molecules; a minority of the pipeline is biologics, and these are generally in earlier stages of development
  - biologics in development for pain include peptide modulators, antibodies, gene therapies, and toxins that target various pain signaling pathways
- Several trends appear in the pain pipeline, such as:
  - abuse-deterrent formulations and other reformulations of opioid drugs and novel opioid MoAs aiming to increase opioid efficacy, reduce side effects and curb opioid abuse
  - novel MoAs aiming to provide longer term, more efficacious and better targeted pain relief

Note: * Includes pain-related indications, such as opioid-induced side effects and anaesthesia adjuncts.
Source: PharmaProjects

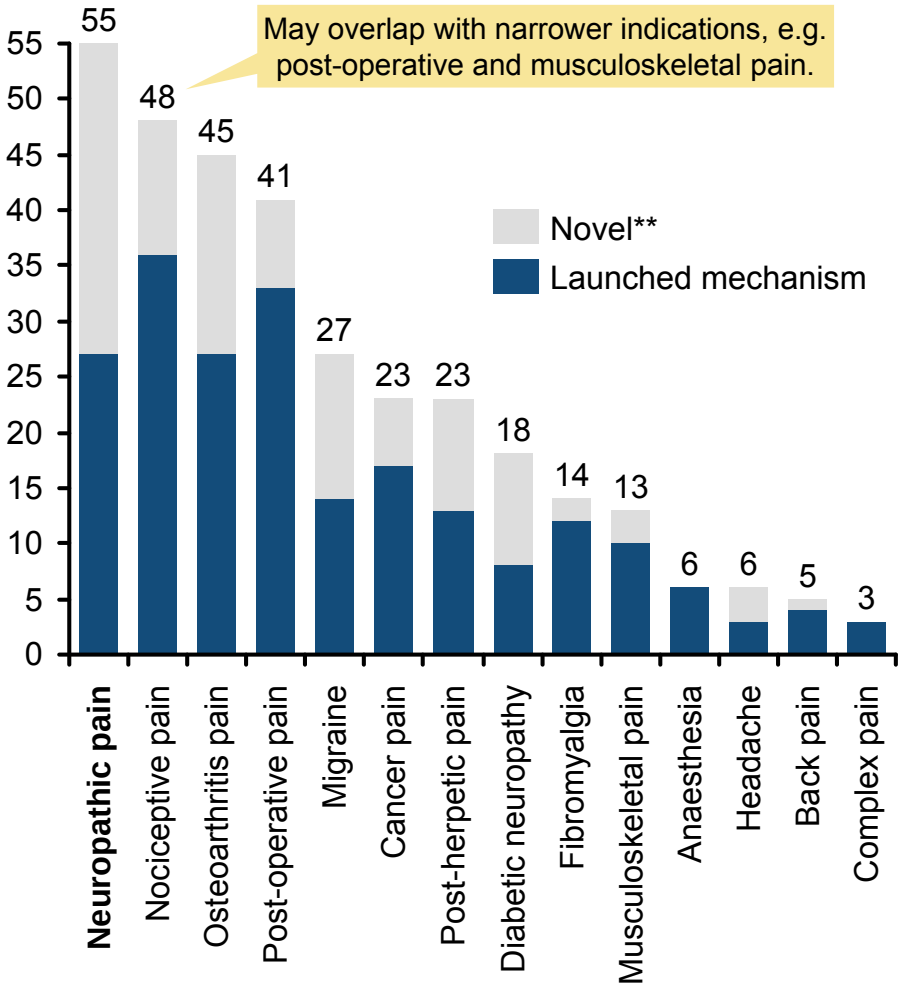
DRAFT

The pain pipeline has a heavy focus on neuropathic, OA and post-operative pain

Overview of the pain development pipeline by indication (February 2016)

Pain pipeline assets in late stage development*

Number of assets



Neuropathic pain is a lead area of interest and investment

Neuropathic pain remains an area of significant interest and industry investment, and the largest segment of the late stage pain pipeline

This is due to the large patient population, chronic nature and high unmet need

There are several reasons for the continued interest in neuropathic pain:

1. *It includes a wide range of pain conditions (diabetic neuropathy, post-herpetic neuralgia, back pain, cancer pain, et~)*
2. *Most neuropathic pain is chronic and long lasting*
3. *Lack of efficacy is a key unmet need in neuropathic pain, so novel therapies that provide complete and continuous pain relief could be blockbuster drugs*

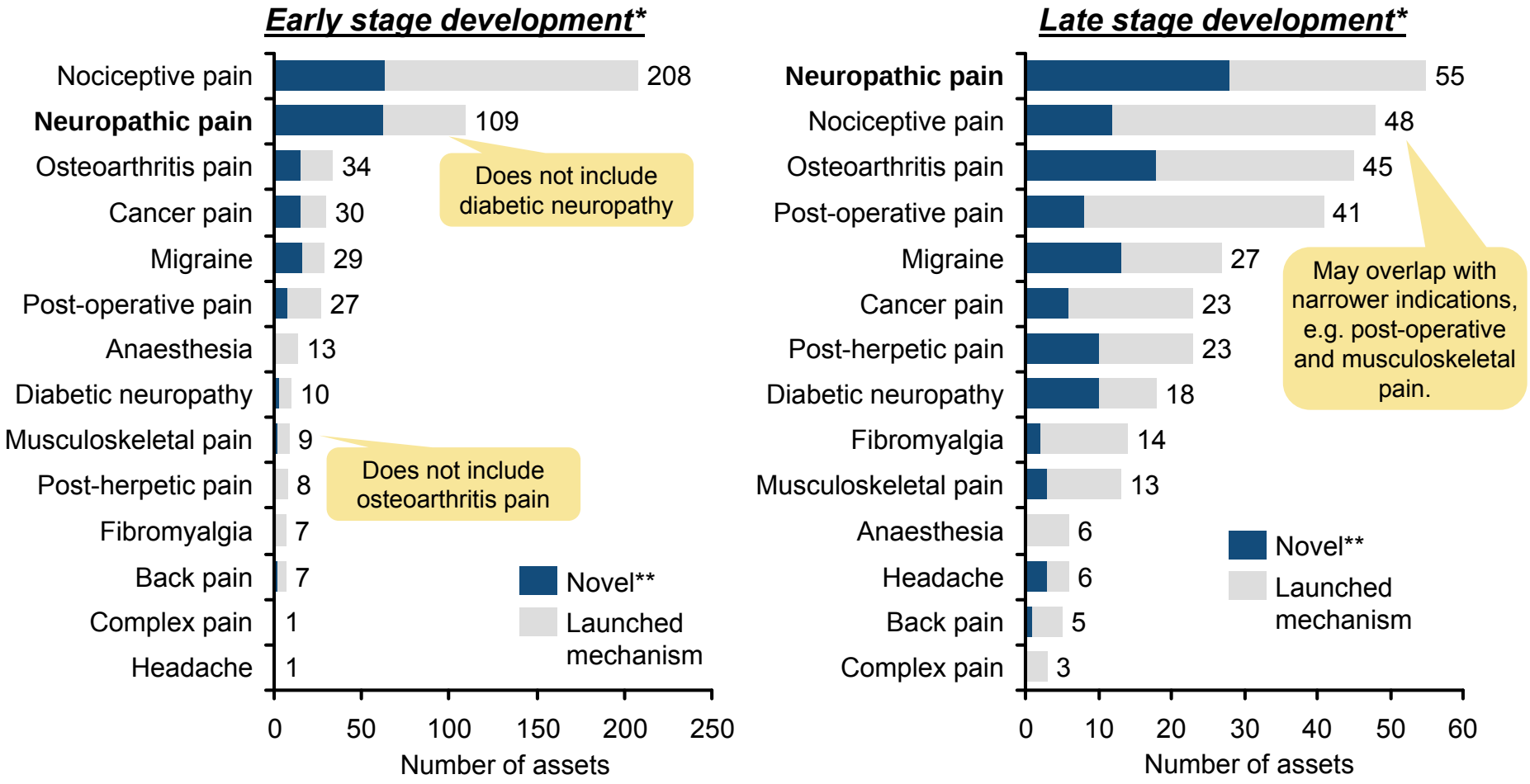
Note * Does not reflect number of unique pipeline assets; one asset may be counted multiple times, if being developed for more than one pain-related indication; ** Assets have been defined as "novel" if no pain products have been launched with the same MoA. Assets in development by Mundipharma/Purdue or related entities are included in this analysis.

Source: PharmaProjects

DRAFT

The pain pipeline has a heavy focus on neuropathic, OA and post-operative pain

Overview of the pain development pipeline by indication (February 2016)



The poorly understood aspects of neuropathic pain management drive high levels of research activity in this area

Note * Does not reflect number of unique pipeline assets; one asset may be counted multiple times, if being developed for more than one pain-related indication; ** Assets have been defined as "novel" if no pain products have been launched with the same MoA. Assets in development by Mundipharma/Purdue or related entities are included in this analysis.

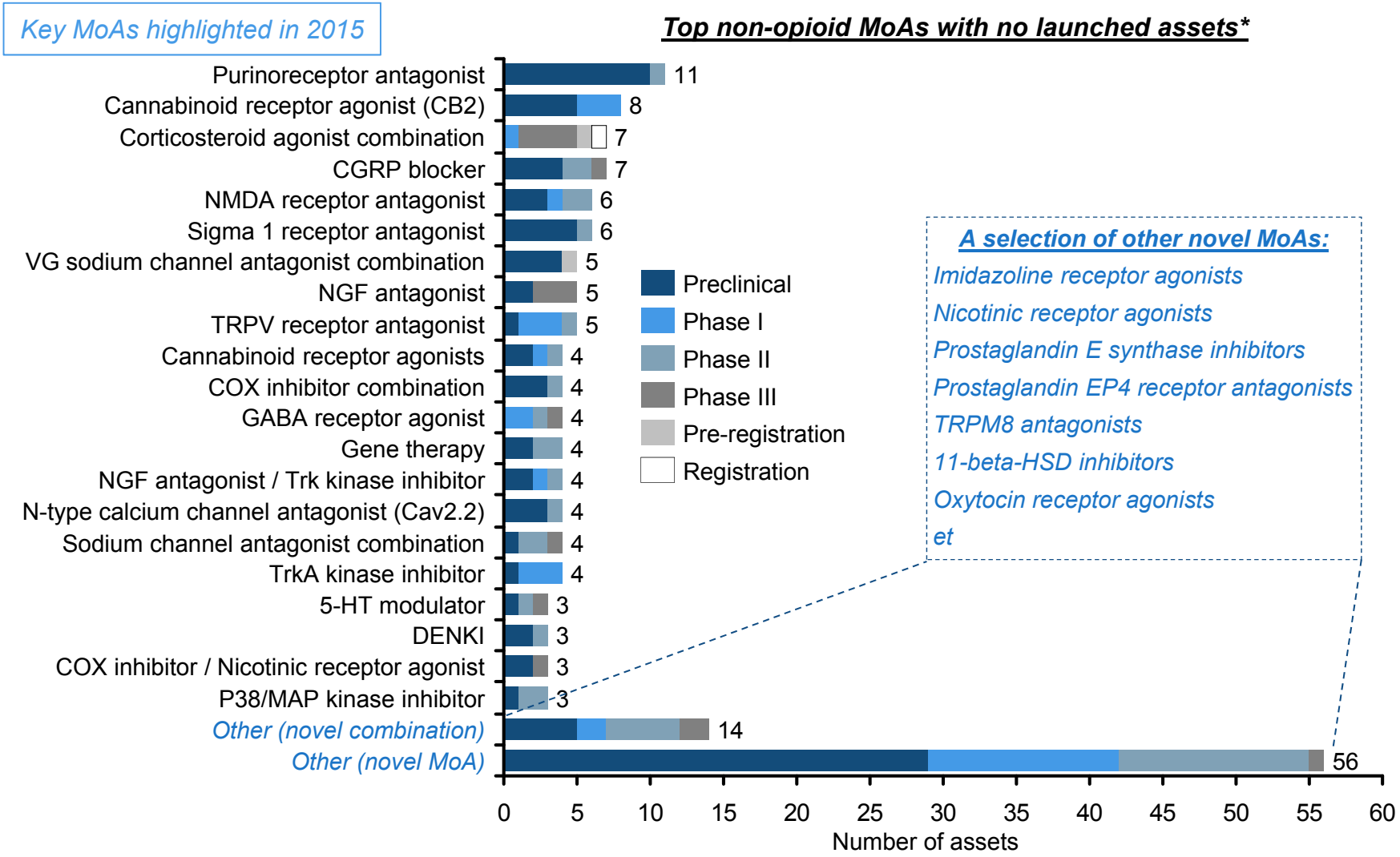
Source: PharmaProjects

DRAFT

Novel non-opioid MoAs and combinations of MoAs in development for pain (*1 of 2*)

Overview of the pain development pipeline by MoA (February 2016)

Key MoAs highlighted in 2015



Abbreviations: 5-HT, 5-hydroxytryptamine receptor; VG, voltage-gated; NGF / TrkA, Nerve Growth Factor Tyrosine Kinase; CGRP, Calcitonin gene related peptide; DENKI, Dual enkephalinase inhibitors; MAP kinase, Mitogen-activated protein kinase; TRPV, transient receptor potential vanilloid.

Note: * Unique assets counted based on latest phase for a pain-related indication. Some assets are combinations of MoAs for which launched products exist, therefore list also includes assets that combine a novel MoA with an older MoA. Such combinations have been included within the segment of the novel MoA.

Source: PharmaProjects

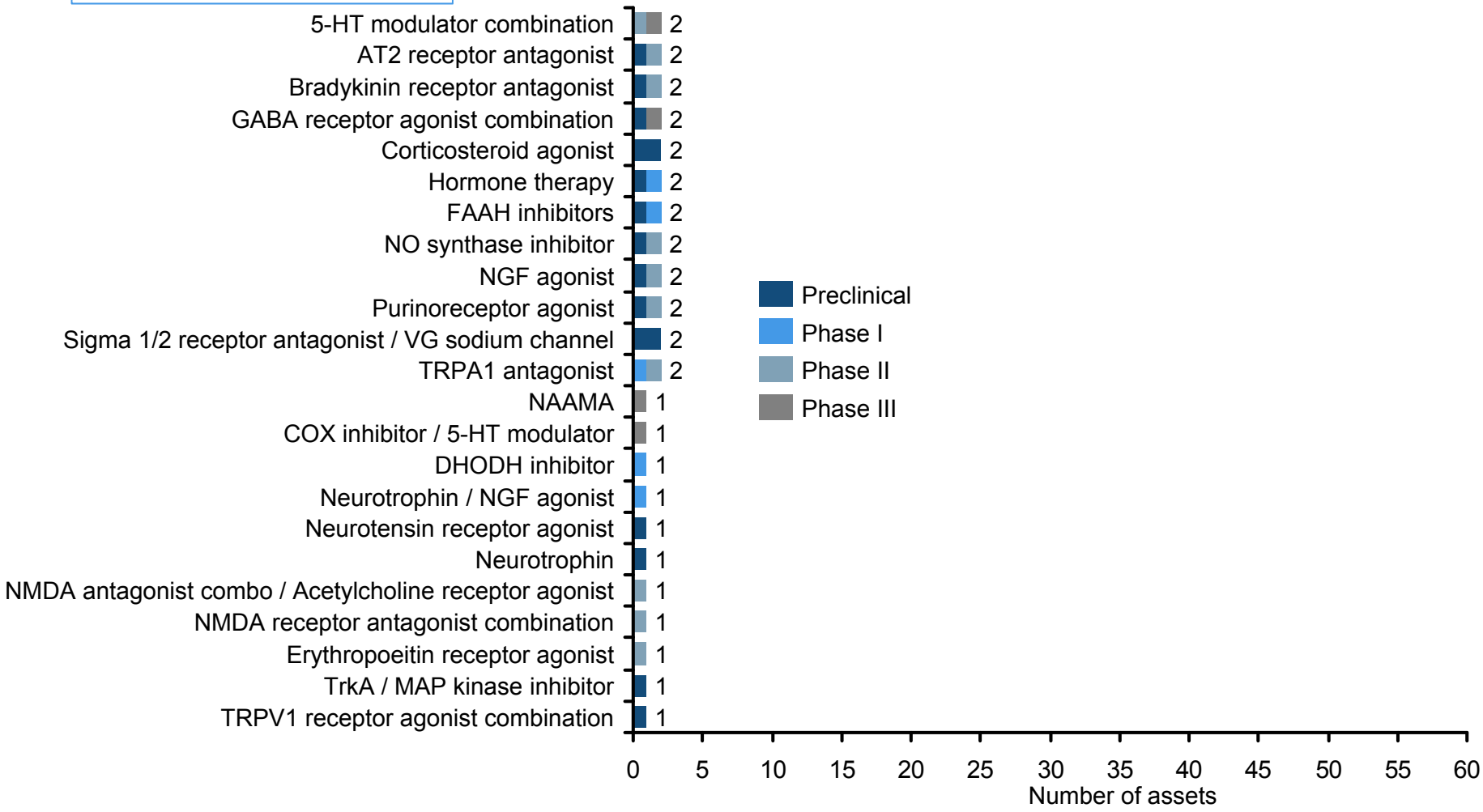
DRAFT

Novel non-opioid MoAs and combinations of MoAs in development for pain (*2 of 2*)

Overview of the pain development pipeline by MoA (February 2016)

Key MoAs highlighted in 2015

Other non-opioid MoAs with no launched assets*



Abbreviations: 5-HT, 5-hydroxytryptamine receptor; AT2, angiotensin 2; DHODH, Dihydroorotate Dehydrogenase; NGF, Nerve Growth Factor; FAAH, Fatty acid amide hydrolase; Mitogen-activated protein kinase; NAAMA, 5-Hydroxytryptamine 1F receptor agonist; TRPA1, Transient receptor potential cation channel, member A1

Note: * Unique assets counted based on latest phase for a pain-related indication. Some assets are combinations of MoAs for which launched products exist, therefore list also includes assets that combine a novel MoA with an older MoA. Such combinations have been included within the segment of the novel MoA.

Source: PharmaProjects

Gene therapies that reduce cellular transmitter and receptor levels or enhance cellular pain modulator levels are interesting developments in the pain pipeline

Inhibition of cellular levels of transmitters and receptors

- Both inhibition and enhancement of synthesis of specific proteins that play a role in the processing of pain stimuli are being considered for chronic pain
- Various studies have reported that **inhibition of cellular levels of transmitters and receptors** in nociceptive processing has an analgesic effect
  - knockdowns of NK1, NMDA, TRPV1, p38 / MAPK, et have been shown to yield analgesia
  - reduction of Nav1.7 (sodium channel) protein levels with siRNA has been shown to reduce hyperpathia in diabetic rats

Enhancement of expression of pain modulators

- At the same time, **enhancement of expression of various pain modulators** through viral and non-viral methods has been found to be analgesic
  - targets include endomorphin-2, IL-10, MAPK phosphatase-1, Kv1.2 (potassium channel)

Examples of gene therapies in the pain pipeline

- There are several gene therapies currently in clinical development for the management of pain. Examples include
  - siRNA for TRPV1 (SYL-1001 by Sylentis) to reduce TRPV1 levels
  - plasmid expression of IL-10 (XT-150 by Xalud Therapeutics) to increase IL-10 levels

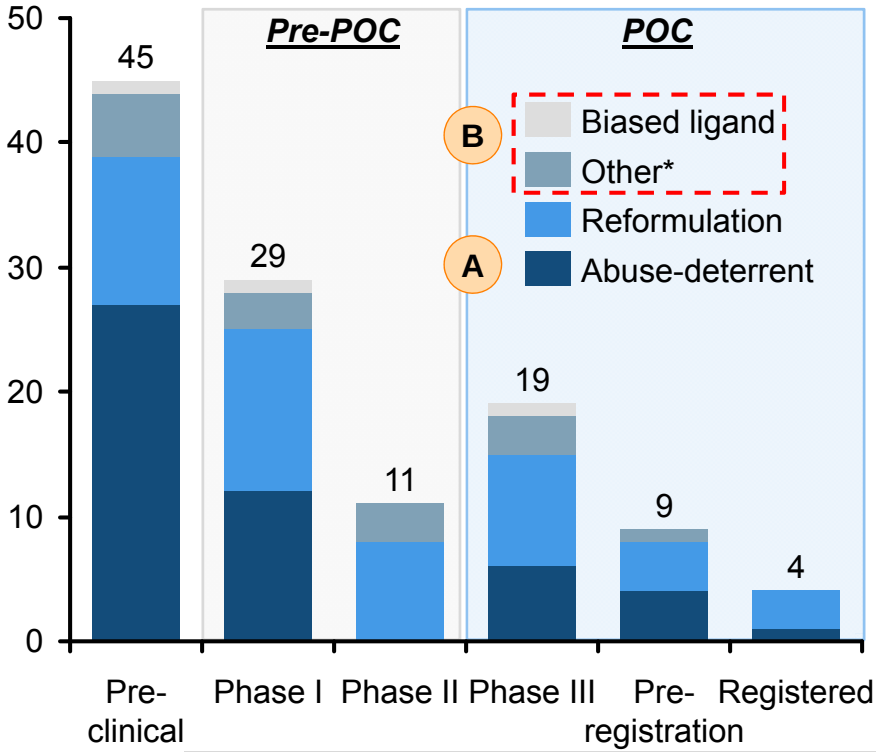
Source: PharmaProjects; Company websites; Yaksh et al. (2015) F1000 Prime reports

DRAFT

Opioids remain ~20% of the pain pipeline, with a move towards reduction of opioid abuse strongly reflected in the current opioid pipeline

Number of unique opioid assets in development for pain (February 2016)

Number of assets



	Pre clinical	Pre-POC	POC
Biased	1	1	1
Other	5	6	4
Reform.	12	21	16
Abuse-det.	27	12	11

Note: * Includes novel opioid MoAs, e.g. peripherally-acting opioids, pan-opioid-receptor agonists, etc
Source: PharmaProjects

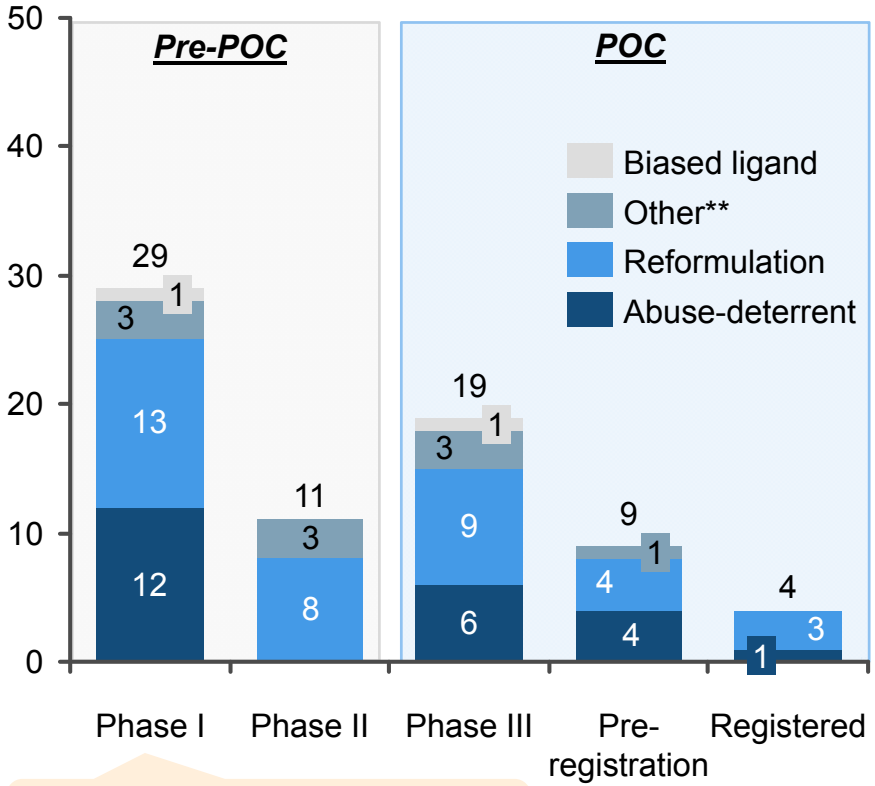
- Opioids make up ~20% of the pain pipeline, with 117 unique novel opioids in development
- The opioid pipeline clearly reflects an aim to transition from older opioid drugs to newer abuse-deterrent formulations
  - most commonly, abuse deterrence is formulation-based, e.g. through a combination of drugs or abuse-deterrent delivery technology
  - less commonly, abuse deterrence is based on entirely new molecular structures
- Non-abuse-deterrent opioid reformulations are usually combinations of multiple drugs that may include non-opioid MoAs
  - these reformulations typically aim to reduce opioid-related side effects and/or provide better efficacy
- In addition to the above, new chemical entities are in development aiming to achieve:
  - better pain relief, including in previously drug-resistant patient populations
  - more targeted pain relief
  - longer-term pain relief with fewer administrations

DRAFT

There is limited innovation in the opioid development pipeline, with a focus on abuse-deterrent reformulations

Number of unique opioid assets in development for pain* (February 2016)

Number of assets



Preclinical is not included due to lack of data on specific MoA

The opioid pipeline clearly reflects an aim to transition to ADFs

The opioid pipeline contains a significant number of ADFs.

ADFs typically utilise a novel abuse-deterrent delivery technology or rely on entirely new molecular structures.

In addition, novel opioids are in development that aim to achieve better, more targeted and longer term pain relief.

Examples of opioid delivery technologies

- LIMITX (acura pharmaceuticals, inc.)
- Trigger Lock (FLAMEL technologies)
- DETERx (COLLEGIUM Pharmaceutical)

Examples of novel opioid molecules

Abuse deterrent

- NKTR-181 (NEKTAR)
- Cyt-1010 (CytogelPharma)
- PF-329 (Ensysce)

- TRV-130 / 250 / 734 (Trevena)

Note: * Includes pain-related indications, such as opioid-induced side effects and anaesthesia adjuncts; ** Includes novel opioid MoAs, e.g. peripherally-acting opioids, pan-opioid-receptor agonists, et

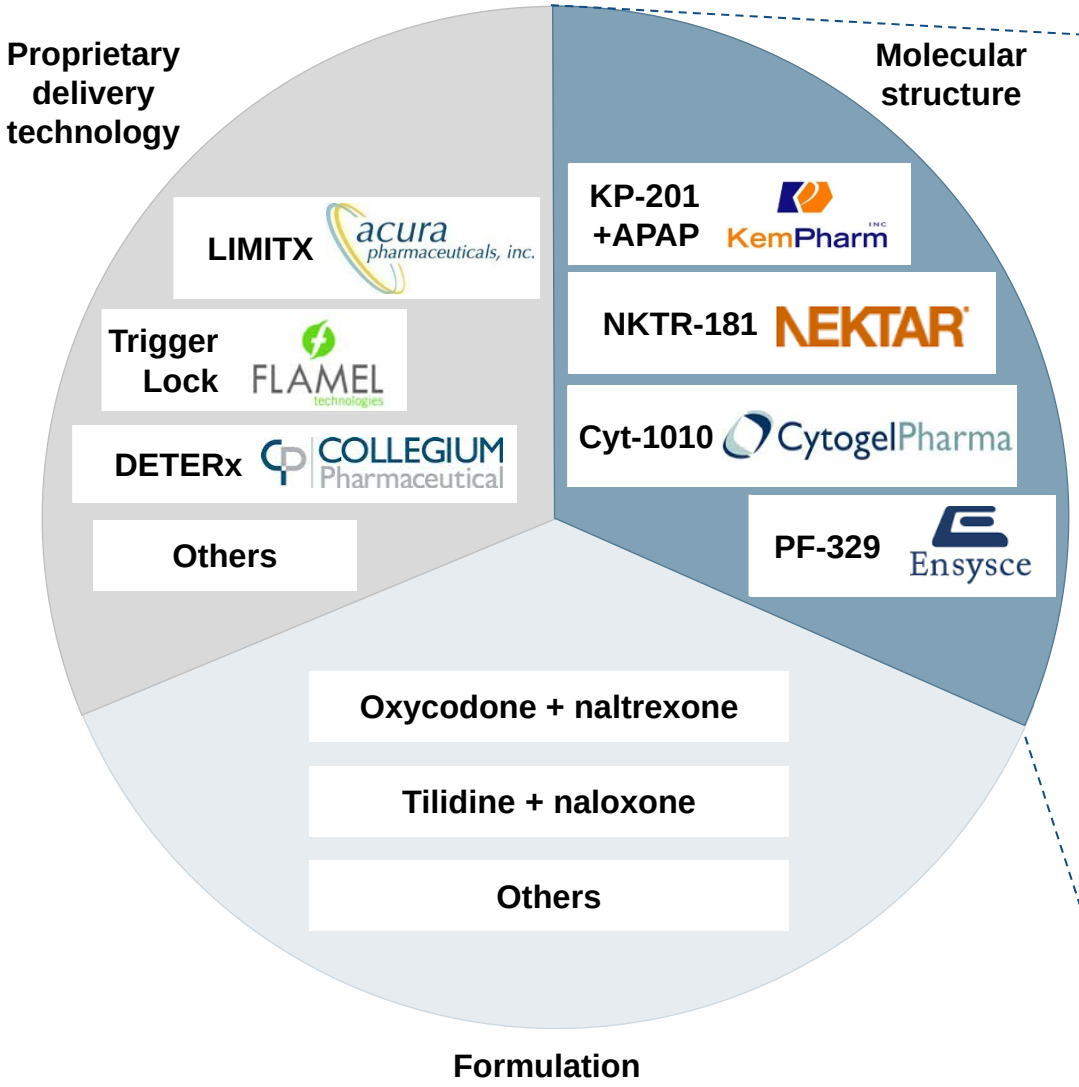
Source: PharmaProjects

DRAFT

Several new ADF opioids are in development, including those aiming to achieve abuse deterrence through their molecular structure

A

Examples of abuse-deterrent opioids and their strategies



- **Pre-registration:**
  - KemPharm's IR combination of KP-201 (benzhydrocodone) and paracetamol aims to curb abuse by selecting a molecular structure that prevents release of the opioid upon tampering
- **Phase III:**
  - Nektar's NKTR-181 has a novel molecular structure designed to enter the brain slower and reduce the euphoria that can lead to opioid abuse
- **Phase I:**
  - Cytogel's Cyt1010, an endomorphin 1 analogue, has shown lower abuse potential than morphine in animal models
  - Ensysce's PF-329 is a novel hydromorphone pro-drug designed to act as a "chemical" barrier to parenteral abuse

Source: Company websites; PharmaProjects

DRAFT

There are also 18 novel non-ADF opioids in development, which aim to increase efficacy, reduce side effects, and target pain relief better

B

Examples of other novel opioids and their strategies

Biased ligand opioids

Better efficacy, selectivity and/or tolerability		Peripherally acting		More targeted pain relief		Other	
Example	**Description**	**Example**	**Description**	**Example**	**Description**	**Example**	**Description**
Cebra-nopadol Phase III GRÜNENTHAL	• ORL1 agonist • High affinity to all 4 opioid receptors • Greater tolerability	**CR-845 (difeli-kefalin)** Phase III CARA THERAPEUTICS	• Peripherally acting kappa receptor agonist	**TRV-130** **TRV-250** **TRV-734** Pre-clinical to Phase III Trevena	• G-protein biased ligands • Preserve therapeutic effect but reduce side effects	**LT-1001 (sebacoyl dinalbuphine ester)** Pre-reg. LIMOSA	• Provides week-long analgesic effect • Does not depress respiratory function
Lexa-nopadol Phase I GRÜNENTHAL	• ORL1 agonist • Synergistic effects with mu receptors	**NKTR-195** Pre-clinical NEKTAR	• Peripherally acting kappa receptor agonist	**PGN-202** Phase II DIAMYD MEDICAL	• Nerve Targeting Drug Delivery system delivers drug directly to the nervous system • Local pain relief	**GIC-1001** Phase II gicare pharma	• Provides sedation-free colonic analgesia
AT-076 Pre-clinical Astraea Therapeutics	• Opioid pan-antagonist • Effective targeting of all 4 opioid receptors	**EU-178** Pre-clinical FERRING PHARMACEUTICALS	• Peripherally acting mu receptor agonist			**SR-105 (omnitram)** Phase I Syntrix BIOSYSTEMS	• New tramadol effective in tramadol-resistant patients

Source: Company websites; PharmaProjects

Appendix

- Market overview
- Asset progress update
- Benchmarking research
- Indication prioritisation research
- MoA research

Lead region:

DRAFT

Lead region:

DRAFT

In-line asset profile: BuTrans/Norspan (2 of 2)

Continuous pain relief with consistent dosing

Commercial characteristics		
Deal structure	*To be filled in by MDP/Purdue*	*[historical revenue & forecast chart]*
Expected / actual peak revenue		
Clinical characteristics		
RoA/dosing	Transdermal 7 day patch; 5µg/h, 10µg/h and 20µg/h doses available	
Efficacy	*To be filled in by MDP/Purdue*	
Tolerability		

Lead region:

To be filled in by MDP/Purdue

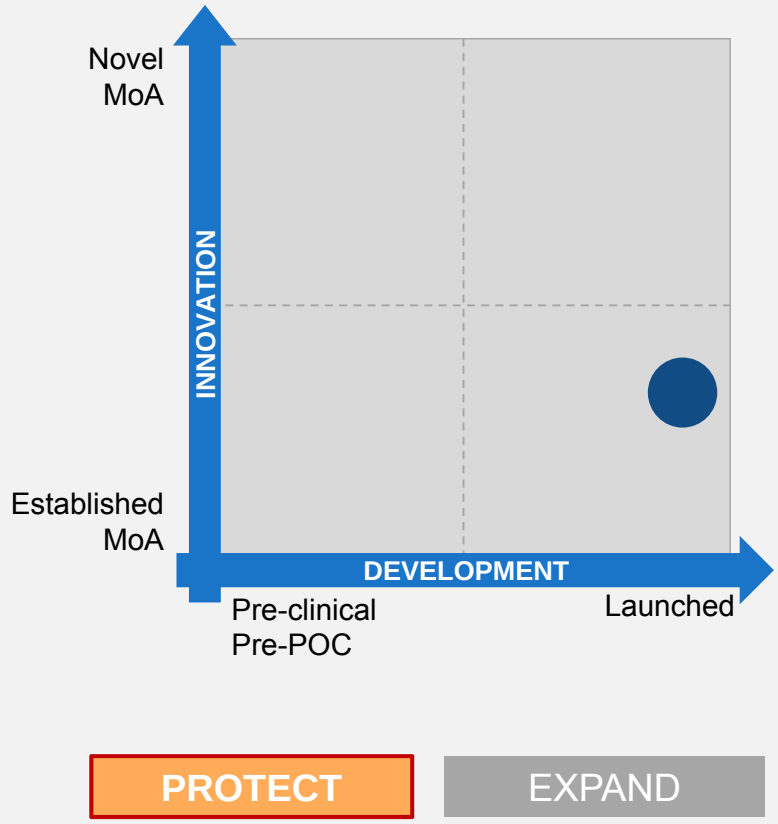
Asset logo

In-line asset profile: *[Asset name]* (1 of 2)

[Elevator pitch / value proposition]

Asset details	
Description	
Company / partner	
Indication(s)	
MoA	
First launch year	
LOE	
Sales	
Market share	
Key value drivers	
Geographies / key competitors	
Next milestone	

Strategic positioning



Source: Management; PharmaProjects; WebMD; Medscape

Lead region: 

To be filled in by MDP/Purdue

In-line asset profile: *[Asset name]* (2 of 2)

Asset logo

[Elevator pitch / value proposition]

Commercial characteristics		
Deal structure		*[historical revenue & forecast chart]*
Expected / actual peak revenue		
Clinical characteristics		
RoA/dosing		
Efficacy		
Tolerability		

Lead region:

To be filled in by MDP/Purdue – one page version

Lead region:

To be filled in by MDP/Purdue – two page version

Lead region:

To be filled in by MDP/Purdue – two page version

Lead region:

To be filled in by MDP/Purdue

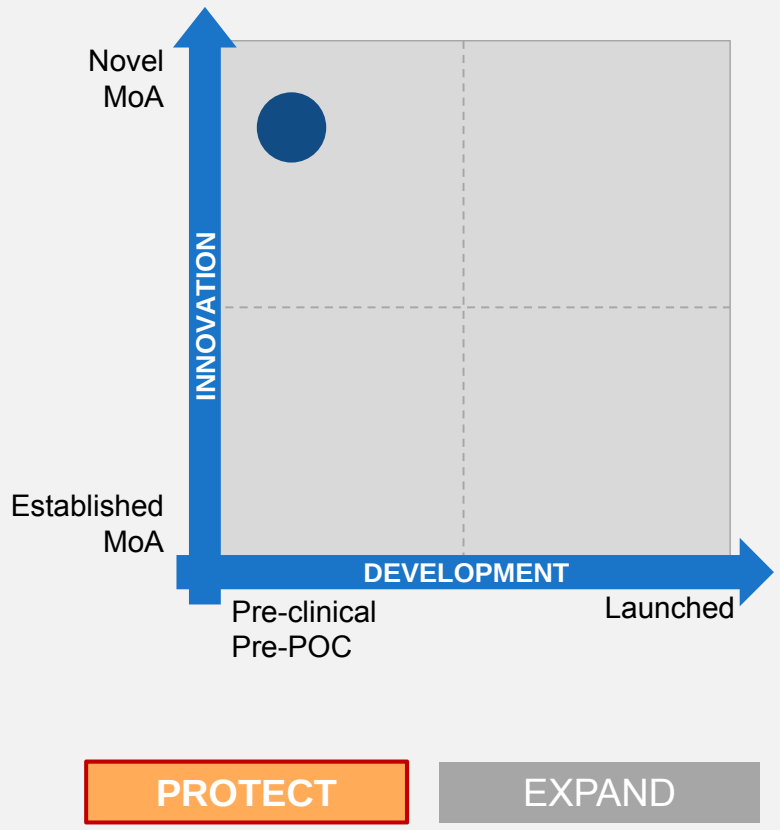
Asset logo

BD asset profile: *[Asset name]* (1 of 2)

[Elevator pitch / value proposition]

Asset details	
Description	
Company / partner	
Indication(s)	
MoA	
LOE	
Key value drivers	
Geographies / key competitors	
R&D cost	
Status	
Next milestone	
Opportunity	
Risks	

Strategic positioning



Lead region: 

To be filled in by MDP/Purdue

BD asset profile: *[Asset name]* (2 of 2)

Asset logo

[Elevator pitch / value proposition]

Commercial characteristics		
Expected deal structure		*[historical and/or revenue forecast chart]*
Expected peak revenue		

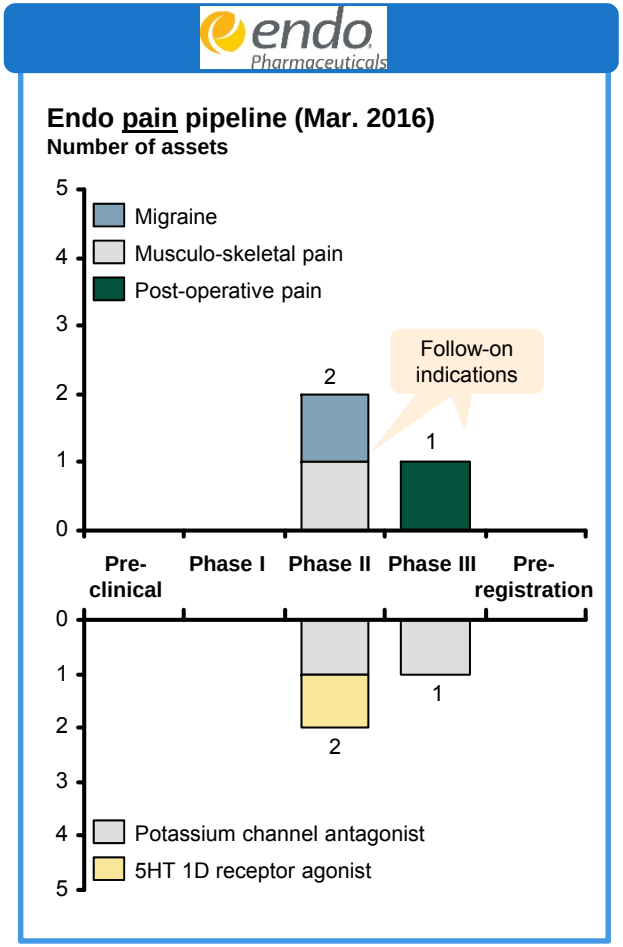
Clinical characteristics		
RoA/dosing		*[trial results / latest data]*
Efficacy		
Tolerability		
PTRS		
Trial design	Phase	
	Location	
	Design	
	Timeframe	

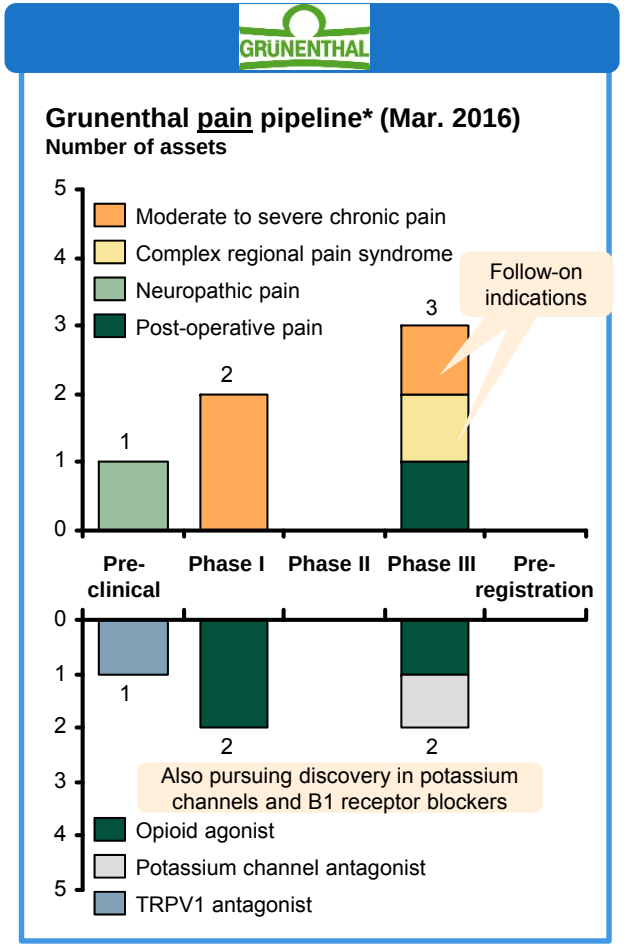
Appendix

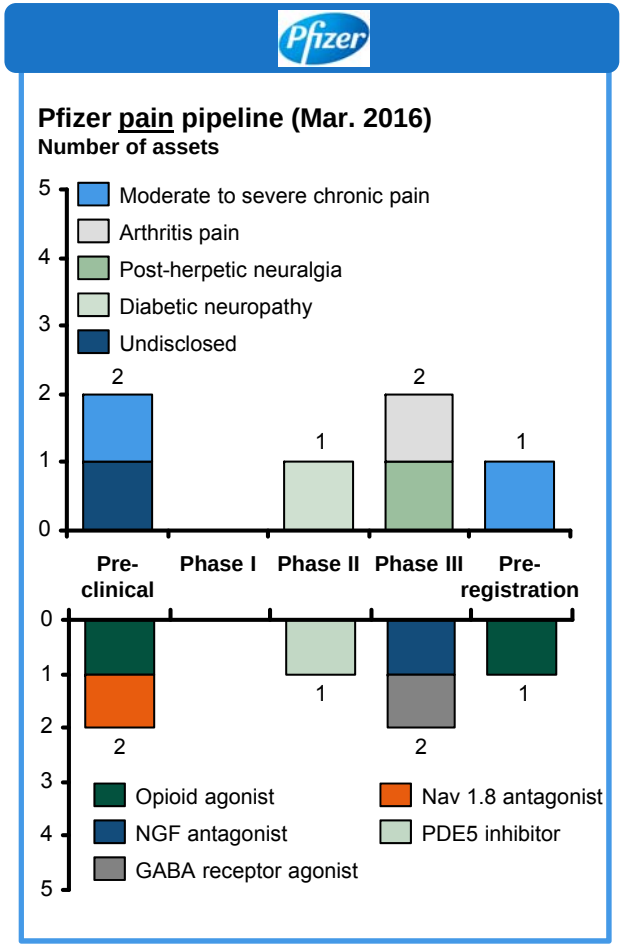
- Market overview
- Asset progress update
- Benchmarking research
- Indication prioritisation research
- MoA research

Refine and incorporate

Competitor pipelines in pain are generally smaller than other TA leaders but are still spread across a breadth of indications and MoAs







The lower number of indications and MoAs in development, along with the more frequent use of a single MoA in multiple indications, underscores the **difficulty of developing innovative targeted therapies** in pain, but **presents us with an opportunity to develop a TA-leading healthy portfolio**

Note: *Grunenthal pipeline is based on publicly available information, but as a private company, Grunenthal may be pursuing additional pipeline projects
Source: PharmaMedTechBI; PharmaProjects; Company websites

Refine and incorporate

TA-leading portfolios focus on core indications while expanding into adjacencies with broadly-applicable products; they build pipelines of 30 products with a significant early-stage presence

Surround core indications with a variety of products across MoAs and lines of therapy	Expand product label to adjacent indications with higher need or lower competition	Develop or acquire new MoAs with broad applicability	Pursue creative approach to demonstrate meaningful value for products
• *Enables us to 'own' our core indications*	• *Maximises the value of our in-line and pipeline products*	• *Maximises probability that asset value can be enhanced post launch*	• *E.g. combination products with improved dosing; trials to be the first product to show a certain benefit*

Benchmarked pipelines consist of ~25-30 compounds with ~40% in preclinical phase and ~25% in Phase II

- *The development and maintenance of a healthy pipeline is a result of acquisitions, collaborations and internal R&D*
- *Portfolio expansion through the acquisition of Phase II and III products diversifies the portfolio and provides opportunities for label expansion and combination products through internal R&D*
- *Co-development of products through partnerships allows the combination of innovative technologies and MoAs as well as geographical expansion*

Refine and incorporate

Other leading pain companies have focused on optimising their key products while expanding into novel MoAs, RoAs and TAs to diversify their portfolio

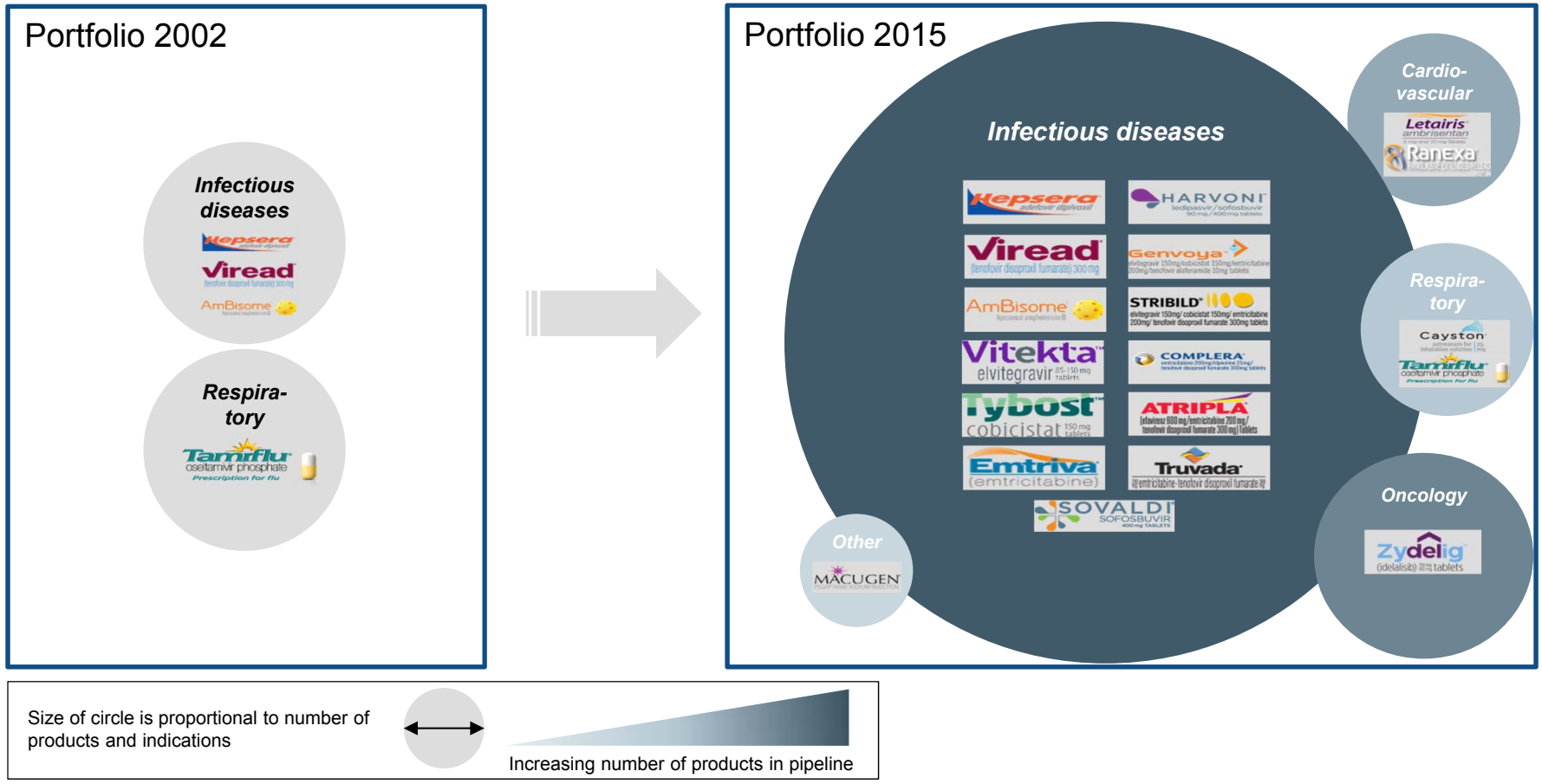
Implement strategy to defend key product before patent loss	Expand portfolio of core strategy products with novel MoAs or RoAs to avoid erosion	Explore adjacent TAs and diversify portfolio
• *Evergreening strategies can extend patent and maintain revenue flow*	• *Enables us to maintain market share following patent expiration*	• *Pharmas may expand from pain to other TAs to enhance their portfolio*
GRÜNENTHAL endo	GRÜNENTHAL endo	Pfizer endo

Refine and incorporate

Gilead became a leader in infectious disease by deepening its HIV and hepatitis portfolio

2002
Small infectious disease portfolio

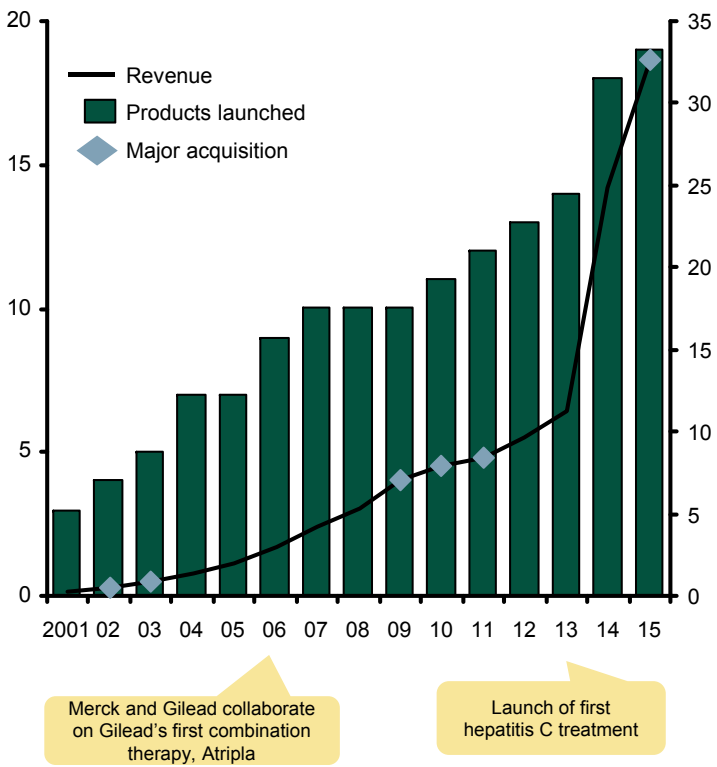
2015
Large HIV and hepatitis portfolio with smaller opportunistic ventures



Source: PharmaMedTechBI; PharmaProjects; Company website

Refine and incorporate

Gilead achieved growth by focusing on addressing large unmet needs and developing a range of products that became leaders in their respective disease areas



Key drivers

Large indication with high need

- Gilead targeted infectious diseases with high prevalence and significant unmet need
- The level of unmet need, coupled with the drugs' ability to prevent costly sequelae to HIV and hepatitis C, enabled high pricing, with total revenues of $30B for HIV and HCV

Lessons for us

Focus on areas of high unmet need and offer a meaningful value proposition

Focus on core indications with range of MoAs

- Gilead entered both the HIV and hepatitis market with a single MoA, reverse transcriptase inhibitors
- Following their success, Gilead expanded the portfolio by introducing other novel MoAs for the same indications, becoming the market leader in each

Surround core indications with a range of MoAs

Expansion via combination products

- Gilead further expanded its portfolio by developing combination products, which offered meaningful improvements such as reducing frequency of administration
- This allowed Gilead to release new products on a nearly annual basis without developing novel drugs
- Now these products dominate Gilead's infectious disease portfolio, with 4/5 top selling products being combinations

Consider opportunities for combination products in key indications

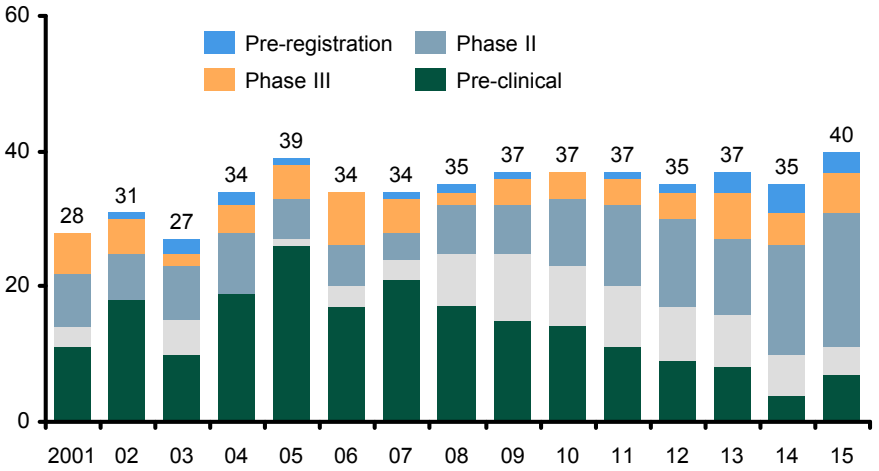
A large but focused portfolio of products allowed Gilead to establish itself as a leader in infectious diseases and to maintain this status through frequent product launches

Source: Bloomberg; PharmaMedTechBI; PharmaProjects; Company website

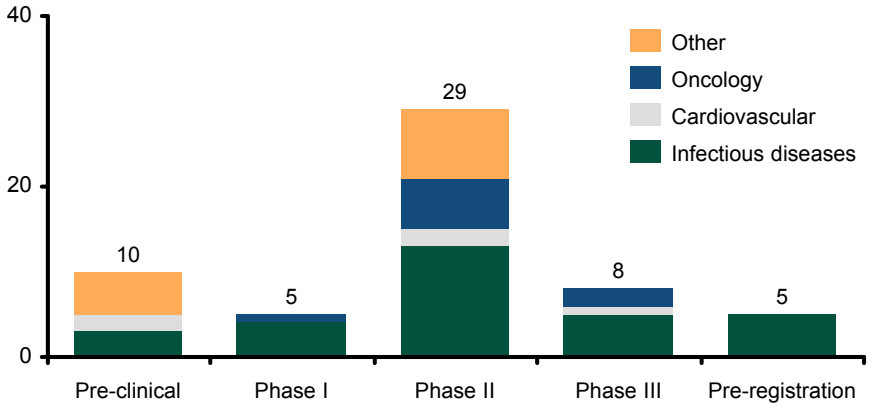
Refine and incorporate

Gilead's growth was driven by a 35-product pipeline, balanced between development phases, as a result of their successful M&A and partnership strategy

Gilead pipeline (2001-16)
Number of assets



Gilead pipeline (Mar. 2016)
Number of assets



- Gilead's pipeline is characterised by strong presence of phase II products, with a total of 57 products in development
  - the average size of the pipeline across the past 15 years has been 35 products, with 40% of products in preclinical phase, 30% in phase II and 15% in each of phase I and III
  - 60% of these products are in infectious diseases
- Gilead has shaped its current portfolio through the acquisition of key assets
  - it entered the HIV market through its merger with NeXstar in 1999 for $0.5B, which gave Gilead access to NeXstar's pipeline
  - Gilead entered the hepatitis C market by acquiring Pharmasset and its Ph III hepatitis C candidate for $11.2B
- Its portfolio of HIV and hepatitis drugs is dominated by products acquired at late stages of development from collaborators, e.g.:
  - emtricitabine from Tibotec
  - rilpivine from Janssen
- Collaborations with large pharmaceutical companies have also allowed Gilead to develop new combination drugs, such as Atripla, and enter developing markets
- Its internal R&D focuses on infectious diseases; however, a significant proportion of its assets is in oncology, which is understood to be an area that Gilead wants to expand into

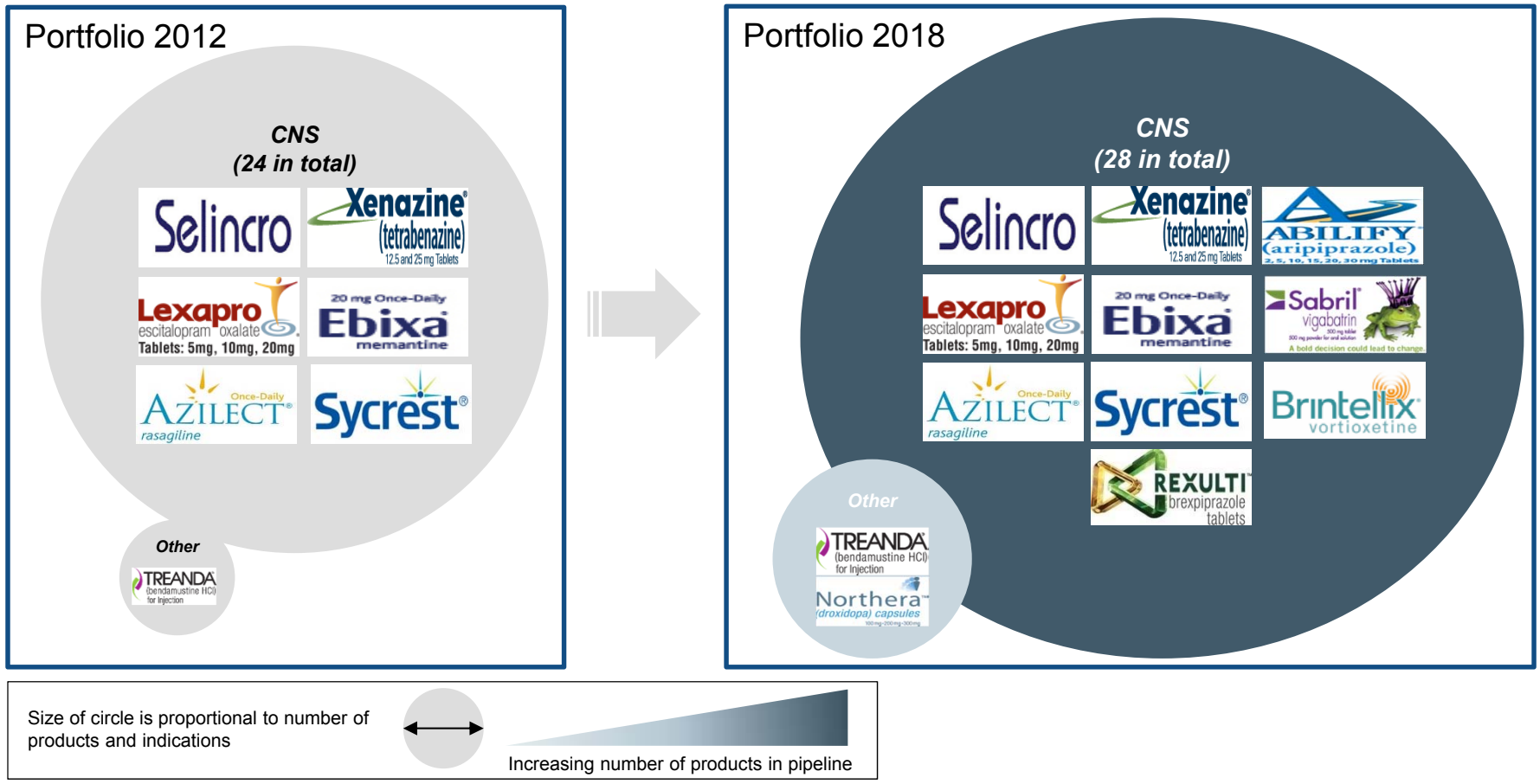
Source: PharmaMedTechBI; PharmaProjects; Company website

Refine and incorporate

Following patent loss of key products from 2013, Lundbeck is expected to return to historical growth through expansion of its CNS portfolio

2012
Large portfolio faces generic competition

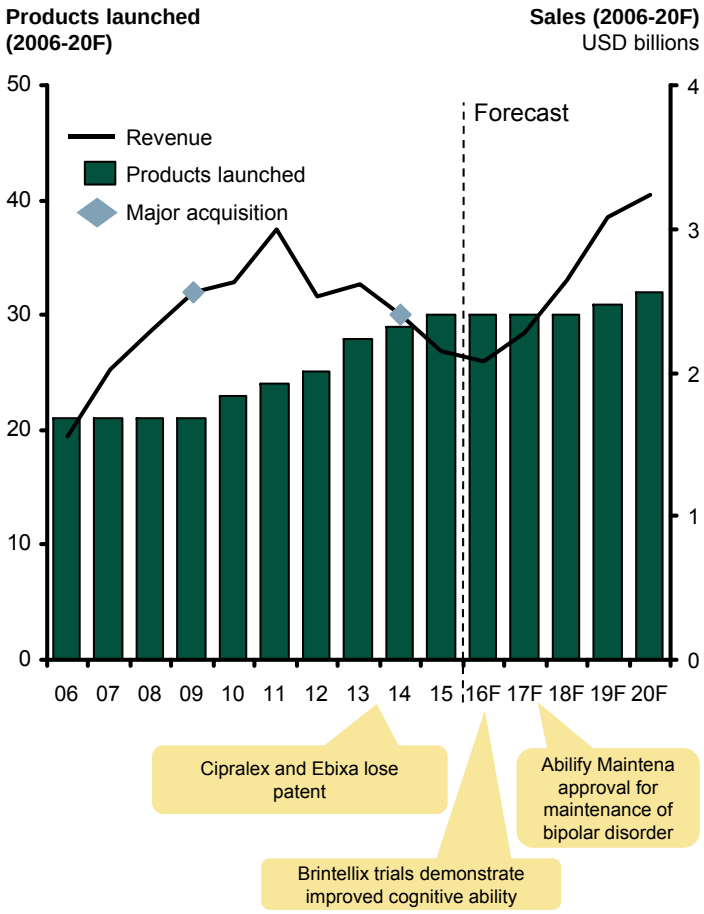
2018
New products expand portfolio and increase sales



Source: PharmaMedTechBI; PharmaProjects; Company website

Refine and incorporate

Lundbeck's forecast growth will be driven by new products and label expansion, which are expected to differentiate its portfolio from generic competitors



Key drivers		Lessons for us
Additional trials add value to drug	• Lundbeck released a novel MoA anti-depressant in 2013 as 1st line treatment for major depressive disorder (MDD), Brintellix, which had a slow uptake • Improvement in cognitive ability with Brintellix is expected to be demonstrated in 2016, highly differentiating the product	Demonstrate harder-to-reach outcomes which increase product value long-term
New products in existing indications	• Lundbeck's Abilify, for psychosis and MDD, went off patent in 2015 • Lundbeck concurrently released Rexulti, which also has a label for psychosis and MDD, with an expected label expansion for maintenance treatment of psychosis • Analysts expect it could gain up to 20% of Abilify's peak share thanks to its claim for better side effect profile and higher potency	Maintain share in genericised indication through evergreening
Reformulated product achieves label expansion	• Lundbeck's Abilify Maintena, a long-acting anti-psychotic, faces competition from other long-acting anti-psychotics • Its sales are expected to increase if it gains a label expansion for long-acting treatment for bipolar disorder, a less crowded field	Expand label to enter less-crowded indications and increase eligible population

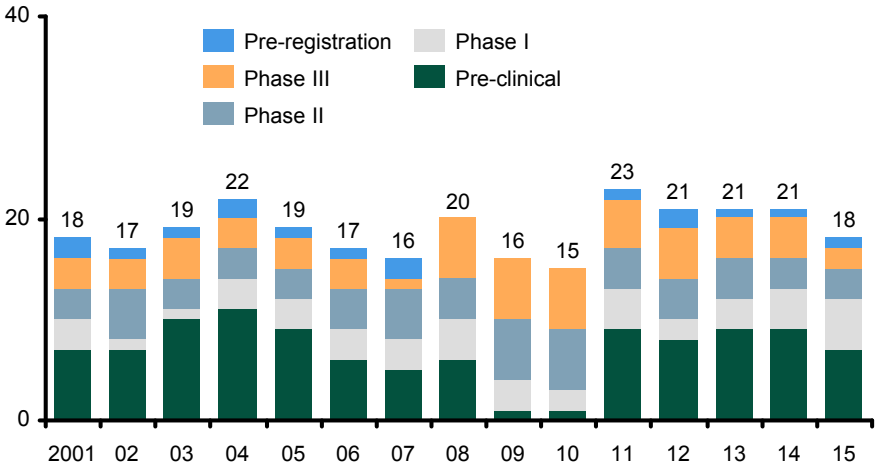
Lundbeck is expected to recover from generic erosion by developing an updated portfolio of differentiated CNS products

Source: Bloomberg; Jefferies; Deutsche Bank; PharmaMedTechBI; PharmaProjects; Company website

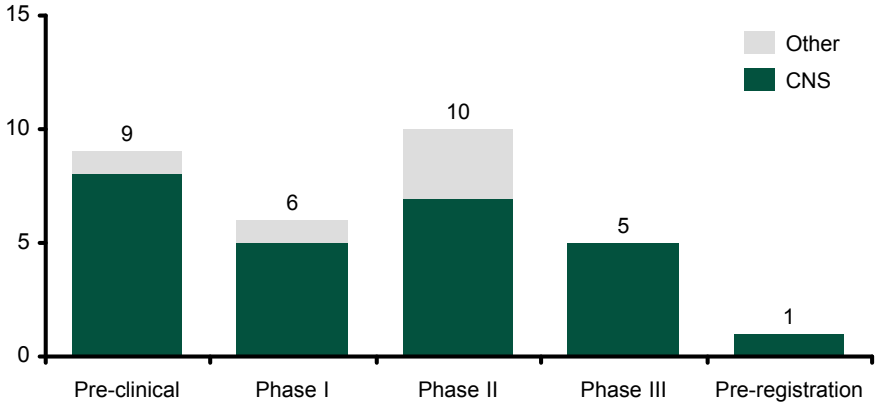
Refine and incorporate

Lundbeck has grown with a pipeline of 30 products spread throughout phases of development, which developed mainly through collaborations

Lundbeck pipeline (2001-16)
Number of assets



Lundbeck pipeline (Mar. 2016)
Number of assets



- Lundbeck's pipeline is spread across all development phases, with a total of 31 products in development
  - the average size of the pipeline across the past 15 years has been 20 products, with 35% of products in preclinical phase and the rest evenly split (15%-20%) between Phases I, II and III
  - 75% of these products are in CNS, with products in other TAs resulting from licence agreements with collaborators (e.g. the licensing of Cephalon drugs in Latin America)
- Lundbeck's pipeline developed through collaborations that led to product co-development
  - through its collaboration with Takeda, initiated in 2007 and worth $0.4B, they developed Brintellix which is forecast to drive future growth of Lundbeck
  - through its collaboration with Otsuka, initiated in 2011 and worth $1.8B, they are expected to co-develop up to five CNS candidates
- Lundbeck acquired strategic CNS assets, completing three acquisitions in a 2009
  - through its acquisition of NeuronIcon it gained access to technology that will allow it to expand its MoAs
  - through its acquisition of lifeHealth and Ovation it expanded its portfolio with tetrabenazine and vigabatrin
- Subsequently Lundbeck divested a portfolio of non-core products as part of its official strategy to focus on newer strategic CNS-products
  - in 2011 three injectable CNS products were divested to Akorn for $85M
  - in 2012 Rercordati acquired non-core CNS and other products for $80M from Lundbeck

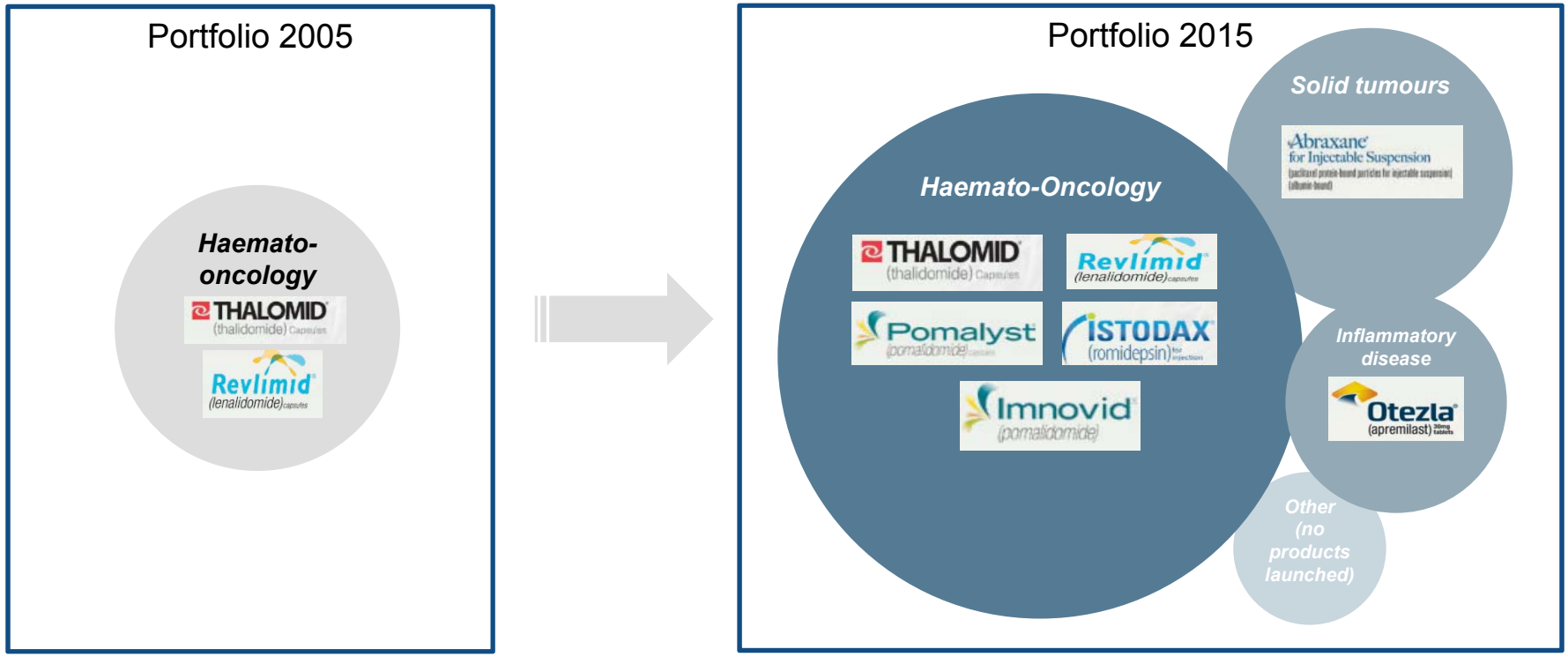
Source: PharmaMedTechBI; PharmaProjects; Company website

Refine and incorporate

Celgene became a leader in oncology by expanding from haemato-oncology to solid tumours before developing a portfolio in its secondary TA, inflammatory disease

2005
Narrow focus on haematological malignancies

2015
Broader focus on oncology and extended product labels



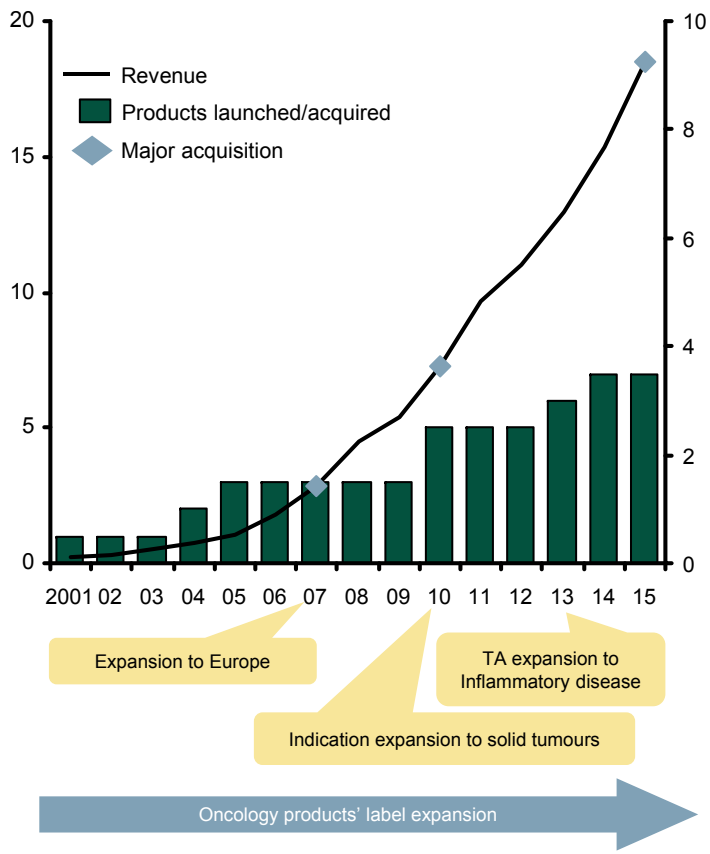
Size of circle is proportional to number of products and indications

Increasing number of products in pipeline

Source: PharmaMedTechBI; PharmaProjects; Company website

Refine and incorporate

Celgene's growth was driven by product label expansion, new product launches, and gradual expansion to adjacent TAs



Key drivers

Label expansion

- Celgene expanded the label of its main products to new lines of therapy and indications, achieving growth without new product launches in the 2005-2009 period
  - e.g. Revlimid expanded from 2nd line to 1st line treatment for multiple myeloma

New MoAs within an indication

- Celgene expanded into new MoAs to develop a portfolio of haemato-oncology products that span entire treatment pathways
  - e.g. Celgene now offers first, second and third-line products in multiple myeloma

Adjacent TA expansion

- Celgene expanded into a second TA, inflammatory disease, with its internally-developed drug Otezla, approved for 2 indications and in trials for 6 more immunology indications
- Celgene's partners and their internal platforms for immuno-modulatory drug development enable drug development in both TAs
  - e.g. 40% of external collaborators offer shared platforms

Lessons for us

- Prioritise opportunities with broad applicability for future label expansion
- Develop new MoAs for failure of treatment in current indications
- Consider opportunistic expansion to adjacent TAs

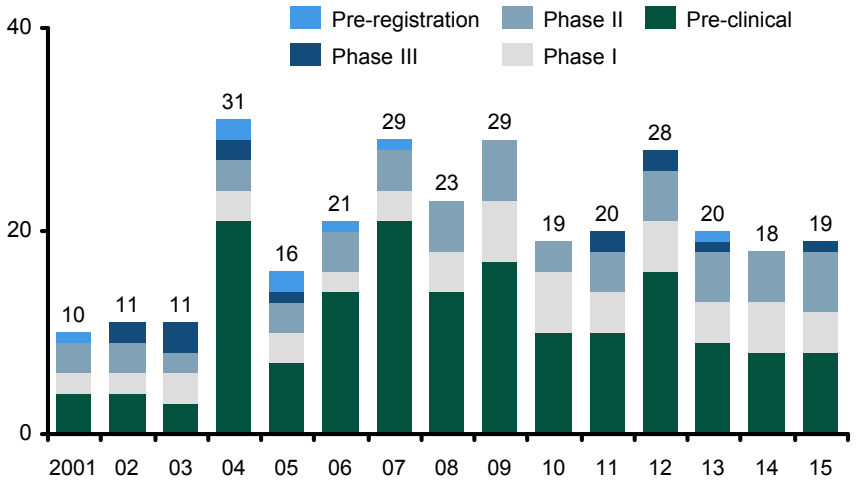
Maintaining an extensive portfolio in one TA whilst expanding to adjacent TAs turned Celgene into a large pharma

Source: Bloomberg; PharmaMedTechBI; PharmaProjects; FierceBiotech; Company website

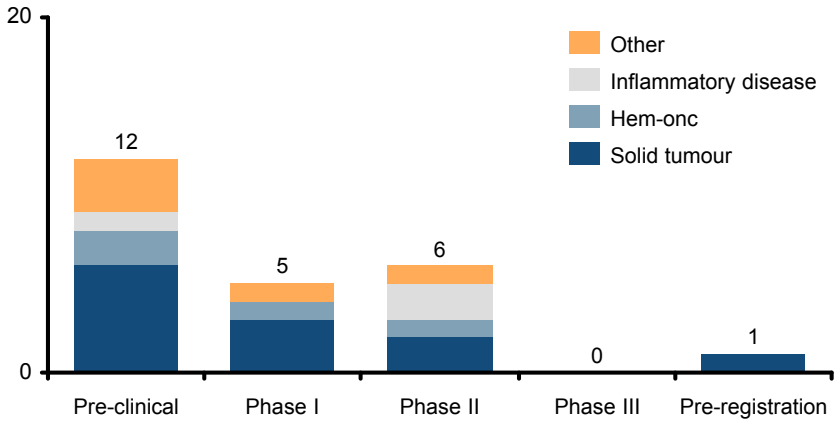
Refine and incorporate

Celgene has now developed a deep 24-product pipeline, largely in partnership with other pharmas, with a wide breadth of MoAs against cancer targets

Celgene pipeline (2001-16)
Number of assets



Celgene pipeline (Mar. 2016)
Number of assets



- Celgene's pipeline focuses on early stage products, especially preclinical and has a total of 24 products in development
  - the average size of the pipeline across the past 15 years has been 22 products, with 50% of products in preclinical phase, 20% in phases I and II and 5% in phase III
  - 50% of these products are in oncology
- Initially a small molecule cancer therapeutics company, Celgene expanded its technology platform and disease focus through major acquisitions, such as:
  - its acquisition of Abraxis in 2010 for $2.9B, through which it acquired the blockbuster-potential drug Abraxane as well as a new platform, a nanoparticle albumin-bound technology
  - its 2015 acquisition of Receptos for $7.3B, through which it gained access to a Phase III product against ulcerative colitis, further expanding in inflammatory disease
- Celgene has also formed partnerships with pharmaceutical companies in order to enhance its portfolio, for example:
  - through its partnership with Array BioPharma in 2007 for up to $500M, it gained access to two undisclosed new cancer and inflammatory disease targets
  - through its partnership with OncoMed in 2013 for $3.3B, it entered the space of stem cell cancer therapy
- In addition, Celgene has continued to invest in internal R&D in small molecules, inflammatory compound inhibitors and enzyme inhibitors, giving it the capacity to develop compounds against multiple cancer targets

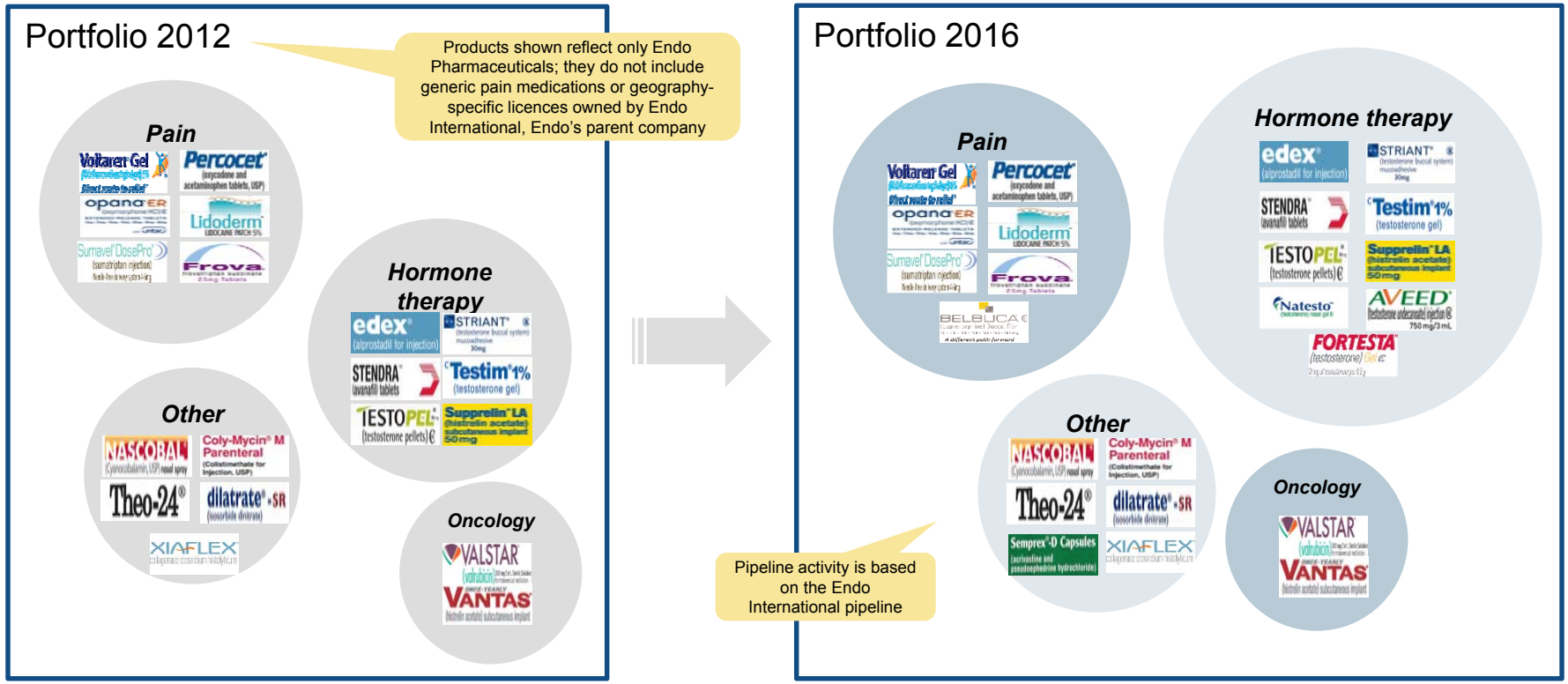
Source: PharmaMedTechBI; PharmaProjects; Company website

Refine and incorporate

Endo has added Belbuca to its pain portfolio and expanded in other TAs; however, Belbuca is at risk of not achieving blockbuster sales like Lidoderm

2012
Mix of branded and generics portfolio

2016
Belbuca is added to pain portfolio and hormone therapies expand

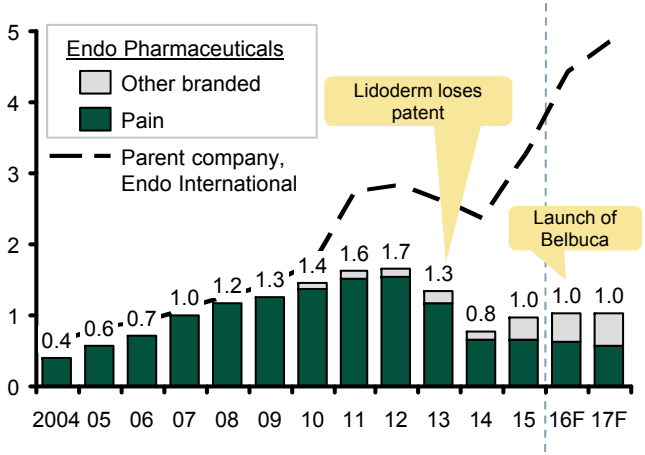


Source: PharmaMedTechBI; PharmaProjects; Company website

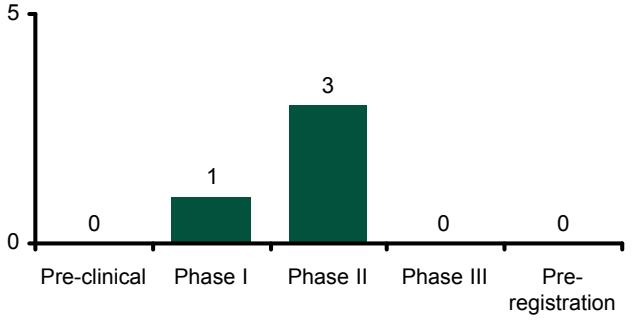
Refine and incorporate

Following Lidoderm's patent expiry, Endo's pain franchise saw significant revenue decline; the parent company, Endo International, diversified to dilute the impact

Sales* (2004-17F)
USD billions



Endo Pain pipeline (Mar. 2016)
Number of assets



Key event		Lessons for us
Lidoderm patent expiry	• Endo Pharmaceutical was primarily driven by Lidoderm, which accounted for more than 50% of revenues • Following patent expiry, Lidoderm lost nearly 90% of its value in 2 years, causing Endo's overall revenues to more than halve 2012-14	Implement strategy to defend key product before patent loss
Belbuca launch drives some growth	• Endo plans to achieve future branded pain growth by launching Belbuca, a long-lasting buccally-delivered opioid used as an add-on therapy in patients with severe chronic pain • The upside case sees Belbuca reaching sales of $500M by 2025; however, competition may delay time to peak and penetration	Expand portfolio of core-strategy products to avoid erosion
Expansion in generics dilutes losses	• Endo International has gone through a series of acquisitions that allowed it to retain and subsequently increase revenues by expanding its pain and non-pain generics business • Generics companies Par, Somar, Paladin, Aspen and Qualtrics were all acquired after 2010, expanding Endo's geographical reach and repertoire of products, including pain and non-pain products	Consider expanding in other TAs to diversify

Endo International invested heavily in acquiring generics companies, which diluted the impact of revenue loss from its pain franchise

Note: *Pain: Sales of top 5 Endo Pharmaceuticals products, Other branded: Sales of top 7 Endo Pharmaceuticals products
Source: Bloomberg; PharmaMedTechBI; PharmaProjects; Company website

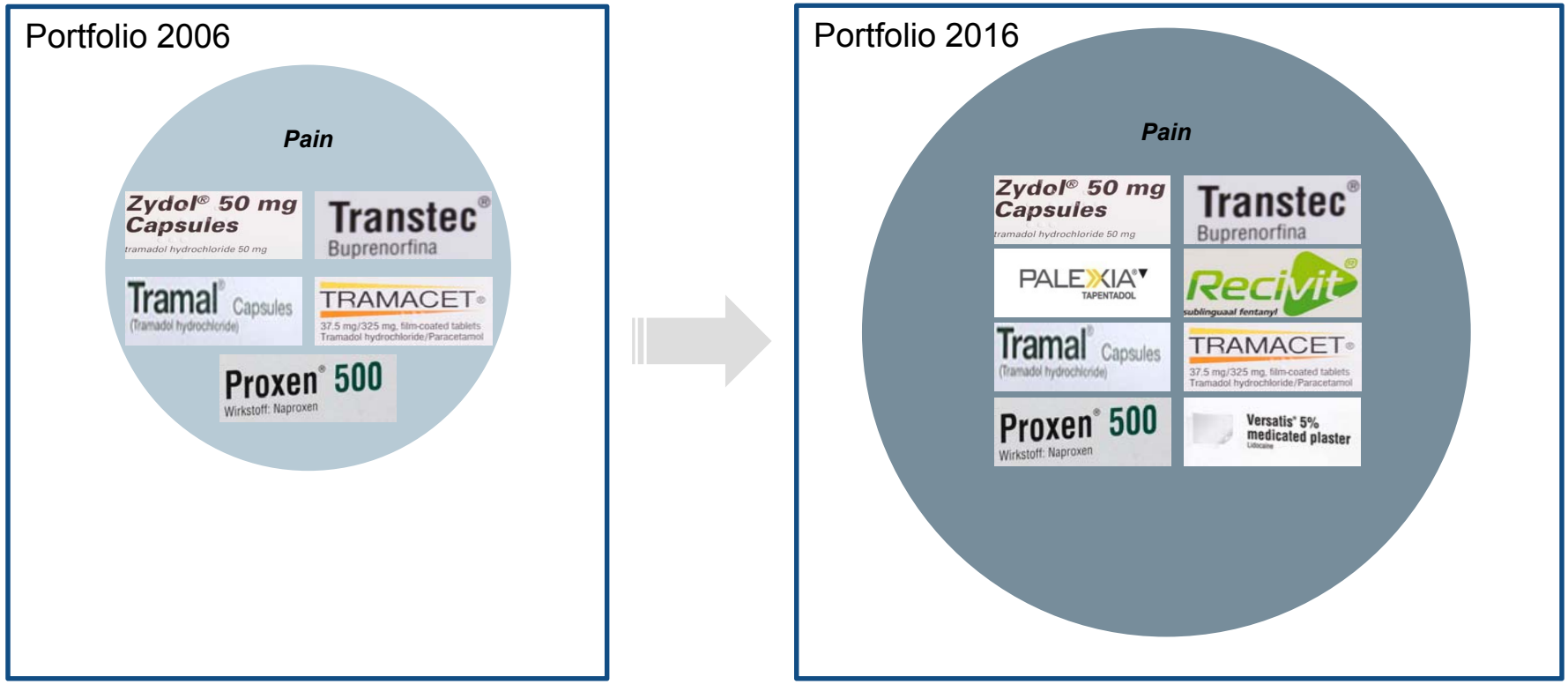
Refine and incorporate

Grunenthal has established itself as the go-to company for licensing pain drugs in European and Latin American countries

Directional and not exhaustive

2006
Pain-focused portfolio

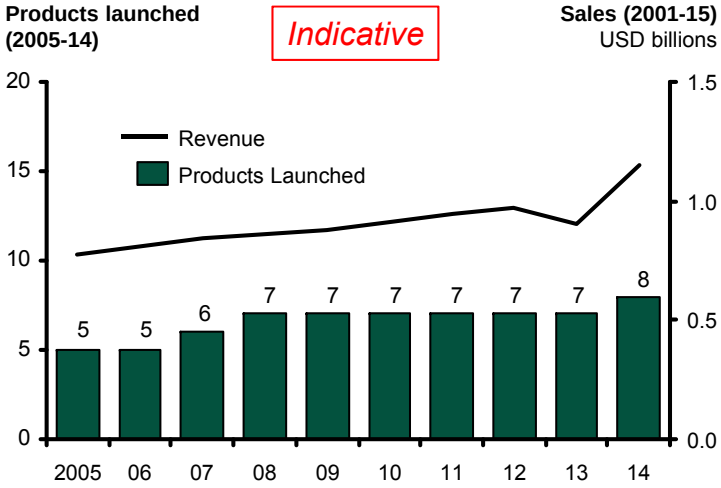
2016
Additional licences for pain

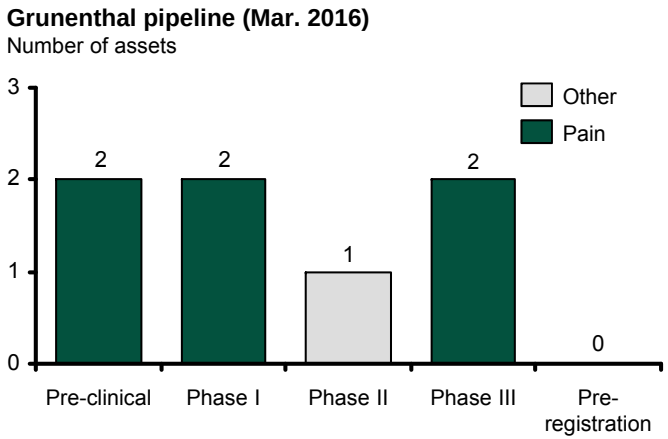


Source: PharmaMedTechBI; PharmaProjects; Company website

Refine and incorporate

Grunenthal is developing opioid and non-opioid analgesics with abuse-deterrent capacity and novel MoAs, beyond acquiring licences from other pharmas





Pipeline features

Abuse deterrent opioid

- Grunenthal is developing an abuse deterrent opioid in collaboration with Johnson and Johnson, currently in phase I
- it is utilising Grunenthal's proprietary technology Intac which offers high mechanical stability and poor solubility

Novel MoAs

- Grunenthal is developing novel opioid and non-opioid MoAs
- The ORL-1/mu receptor agonist currently in Phase I is developed in collaboration with Forest Labs
- Grunenthal is also developing a product for neuropathic pain, a TRPV1 antagonist currently in preclinical stage

Non-pain products

- Grunenthal is developing a single non-pain product, in collaboration with Akashi Therapeutics, against Duchenne Muscular Dystrophy

Lessons for us

- Emphasise significance of Mundi / Purdue ADT strategy
- Continue to develop multiple MoAs for range of indications
- Consider opportunistic expansions on neighbouring indications/TAs

Grunenthal is developing a small but broad pain pipeline, largely supported by collaborations

Source: PharmaMedTechBI; PharmaProjects; Unternehmensregister; Company website

Appendix

- Market overview
- Asset progress update
- Benchmarking research
- Indication prioritisation research
- MoA research

Change NAMSP to OA/chronic lower back pain (or something similar)

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

Neuropathic pain

DRAFT

Neuropathic pain represents a substantial potential opportunity, characterised by significant unmet needs in treatment with a large and growing patient population

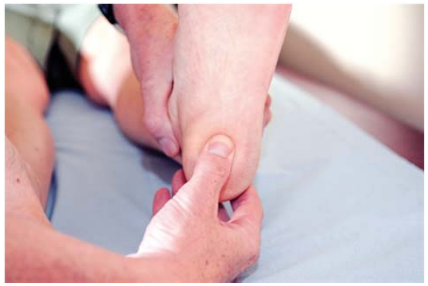
Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• Current treatments are largely ineffective, with very few patients obtaining complete pain relief. Physicians cite lack of drug efficacy as a key unmet need, which is the primary cause for treatment switching
Validation of disease & treatment		20%	• Diverse aetiology with complex variations in underlying pathophysiology. However, significant scientific progress has been made in understanding the condition, leading to potential new targeted therapeutic approaches
Competitive intensity		10%	• Treatment options are limited and broadly ineffective. There are 230 unique pipeline compounds although no asset is expected to significantly impact So~ Lyrica patent expiry in 2018 likely to lead to strong generic competition
Market opportunity		10%	• Neuropathic pain has an incidence of 8%, indicating 160m patients in Mundi/Purdue's markets. Prevalence is expected to grow as growing diabetes prevalence rates result in more cases of diabetic neuropathy
Probability of clinical trial success		10%	• Regulatory success can be achieved by showing efficacy on simple rating scales, with favorable safety. Trial endpoints vary, relying on patient-reported outcomes with no regulatory or clinical gold standard
Overall attractiveness			• ***High unmet needs and strong future demands.*** NP incidence is likely to increase concurrently with global diabetes prevalence. Current treatment efficacy is limited and unsatisfactory, and opportunities may arise for novel compounds and MoAs that target underlying disease pathophysiology

Neuropathic pain

DRAFT

NP is a widespread condition with 160m sufferers globally, with patient populations forecast to grow due to increase in prevalence of underlying conditions, e.g. diabetes

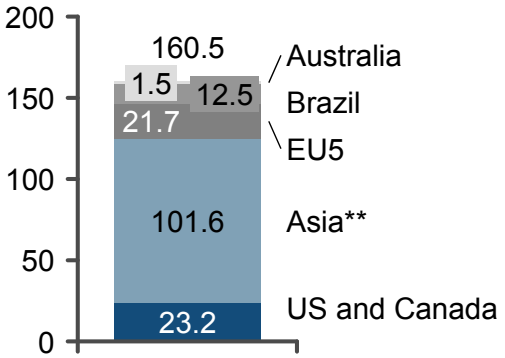
Indication overview



- Neuropathic pain (NP) is caused by a primary lesion or dysfunction in the nervous system
- Pain may result from diseases of the nerve (e.g., post-herpetic neuralgia) or from the side effects of systemic illness (e.g., diabetes, trauma or chemotherapy-induced neuropathy)
- The largest indications within NP include neuropathic lower back pain (NLBP) and diabetic peripheral neuropathy (DPN)
  - NLBP is typically the result of a pinched nerve but has several potential causes
  - DPN is a family of nerve disorders caused by diabetes and presents as numbness, weakness and sometimes pain in the hands, arms, feet, and legs
- Other sensations associated with neuropathic pain include tingling, burning, freezing and sensitivity to touch
- Here, NP encompasses diabetic neuropathy, post-surgical neuropathy (may include phantom limb pain), postherpetic neuralgia and broad neuropathic pain (including NLBP)
- Chemotherapy induced NP is covered within cancer pain

Epidemiology

Prevalence of NP (2015)
Millions of patients*



INDICATIVE

Prevalence varies widely by geography and underlying disease, with 8% used as the global mean for broad NP indications

- General population studies, using validated screening instruments, have found that 8% of adults currently have chronic pain with neuropathic characteristics
- Studies do vary between 2-11% depending on methodology and geography, but the IASP 8% consensus is used here
- Prevalence in specific patient populations varies by aetiology:
  - 18-26% of diabetes patients suffer from DPN, with prevalence set to double by 2030 with diabetes growth rates
  - an estimated 35% of patients suffering from HIV and 37% suffering from herpes virus infection suffer from NP
  - 10% of patients will develop NP post surgery
- Age and length of time diagnosed with underlying condition are the primary factors driving epidemiology

Note: * Estimated based on population above 15 yo. ** Includes Malaysia, China, Singapore, Philippines, South Korea. ^ ACR: American College of Rheumatology
Source: International Association for the Study of Pain (IASP); Datamonitor

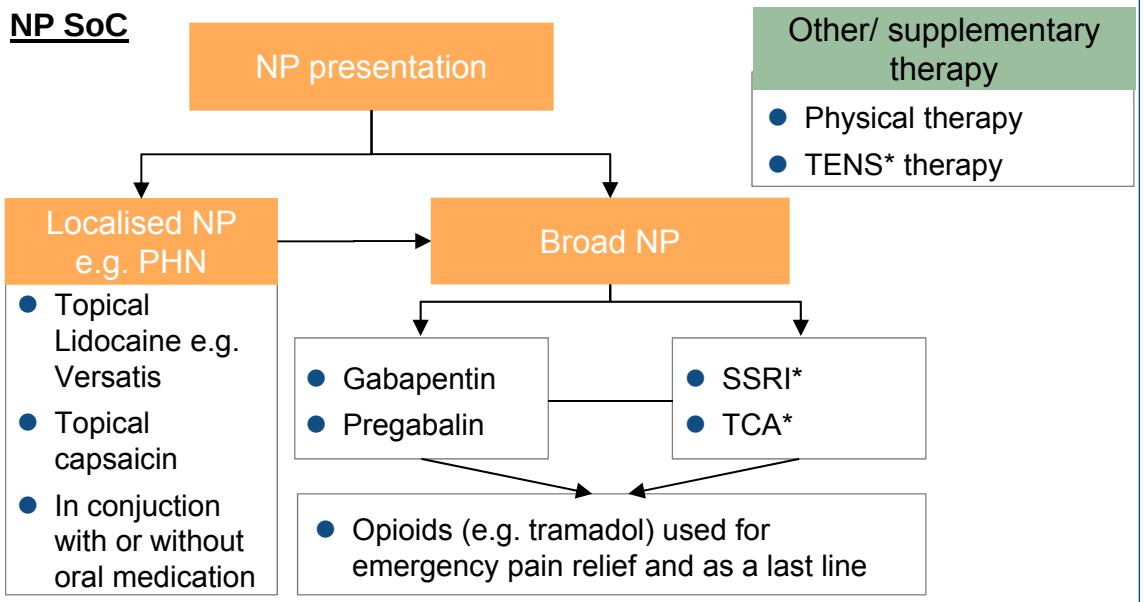
DRAFT

The complex aetiology and heterogeneity of underlying conditions means current NP treatments are largely interchangeable with limited consensus on treatment approach

Disease aetiology / pathophysiology

- NP is caused by neural dysfunction stemming from extensive molecular changes in the neuron arising after nerve injury, either directly or due to underlying clinical condition
- This leads to central sensitisation through a wide variety of electrophysiological, molecular and anatomical changes, which is largely responsible for prolonged pain and allodynia
- Due to the large variety of mechanisms involved, there is significant variation in patient symptoms, treatment responses and outcomes
- Although most pathophysiological knowledge of NP stems from mouse models, there has been a significant increase in our understanding in recent years
  - the role of upregulation of voltage gated sodium channels, the characterization of the potential involvement of other druggable targets such as adrenoceptors, acid sensing ion channels and heat sensitive receptors are a few examples of scientific advances in NP

Current treatment paradigm



- First line options in NP guidelines only discriminate between localised (i.e. post-herpetic neuralgia) and other NP, largely due to relative effectiveness of localised treatment in these conditions
- For broad NP, guidelines do not discriminate between anti-epileptics and antidepressants as first line therapy
- Guidelines recommend switching between the remaining three drugs in case of low efficacy or poor tolerability
- Tramadol is only primarily used as acute rescue medication

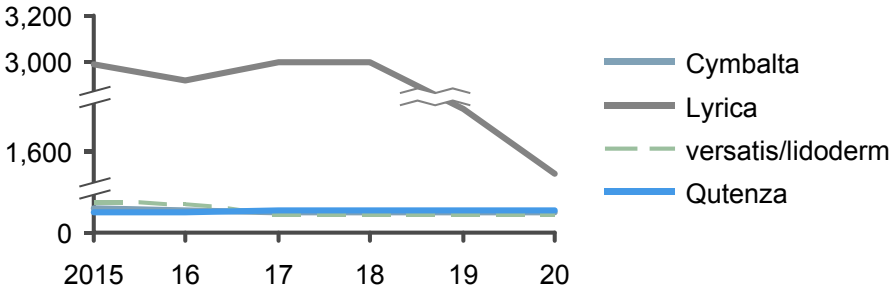
Note: * TENS: Transcutaneous electrical nerve stimulation; SSRI: Serotonin specific reuptake inhibitor; TCA: Tricyclic antidepressant
Source: IASP NP Fact Sheet, NICE NP guidelines, Finnerup et al (2007) MedGenMed, Dworkin et al (2010) MayoClinic Proceedings, Baron *Nature Clinical Practice Neurology* (2006)

DRAFT

Unmet needs in NP arise primarily from the inability of existing treatment to adequately control pain for the vast majority of patients, leading to challenges for all stakeholders

Currently marketed treatments

Projected sales for key marketed products (2015-25)
Millions of dollars



- There are only five FDA and EMA-approved drugs to treat NP
- Gapabentin reformulations Gralise (extended release, Depomed, 2011) and Horizant (gabapentin enacrabil, XenoPort, 2012) are also approved for post-herpetic neuralgia
- Nucynta ER (extended release tapentadol, J&J) was approved by the FDA in 2012 for diabetic neuropathy with predicted peak sales of 900m USD in 2019

Name (generic)	Marketed by	Patent expiry	Class
Lyrica (pregabalin)	Pfizer	2018	Anti-epileptic
Gabapentin	Multiple	n/a	
Cymbalta (duloxetine)	Eli Lilly	Expired	Anti-depr.
Versatis/Lidoderm (lidocaine 5% patch)	Greunthal (EU) Endo (US)	Expired	Topical local anaesthetic
Qutenza (capsaicin 8% patch)	Acorda	2016	Non-opioid

Key unmet needs

- Physicians cite **limited response to and efficacy of treatments:** in RCTs of pharmacologic therapy for NP, no more than 50% of patients experience clinically significant (30-50% reduction) pain relief, and in those who respond, pain is almost never fully relieved
- Physicians also cite **limitations to the duration of efficacy** of most treatments, and patients continue to have moderate pain despite taking treatments
- **Treatment can be burdensome** with side effects such as drug-drug interactions, CV side effects and CNS side effects for antidepressants/antiepileptics and dizziness and application site reactions for transdermal patches
- There is a **lack of clinically meaningful efficacy data**, as there are few head-to-head clinical trials and the duration of treatment in most trials (typically 3 months) does not reflect the chronic nature of NP, making it difficult to make evidence-based treatment decisions
- **Unpredictable and subjective nature of patient response to treatment**, combined with high patient burden of chronic pain, can lead to negative stigma and lack of trust for patients in physician ability to treat
- Due to lack of appropriate clinical data and consensus on analgesic superiority, payors have unmet needs in **making informed budgetary decisions**

Note: * NNT: Number needed to treat
Source: EvaluatePharma; nature reviews drug discovery; Kantar Health Patient Journey in DNP; Moore et al Cochrane Database Syst Rev, 2009/3

DRAFT

Although there are a large number of assets with diverse MoAs in the development pipeline, none are expected to dramatically alter the treatment paradigm in the near term

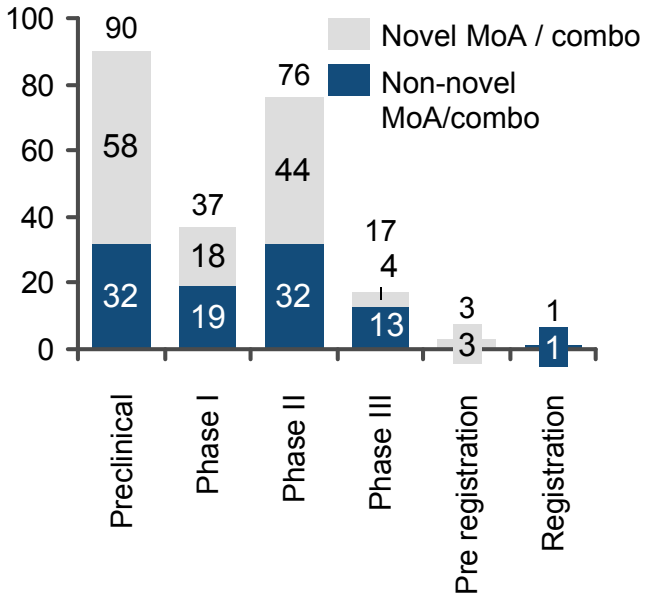
Typical clinical trial design, timing, size

- Primary efficacy endpoints in late stage NP trials are subjective instruments including PRO* measures and pain diaries, such as
  - 10 point rating scales
  - Visual analogue scales
  - ADL*
  - SF-36*
- FDA guidance recommends a rating scale and using 'well defined and reliable PRO measures'
- Nearly all trials are compared vs. placebo, and the wide array of different PRO rating scales and end points make indirect comparisons difficult
- Typical PhIII trials include 300 patients, with dosing duration between 4 -12 weeks

Phase**	Avg enrolment	Avg length (mo)
I	50	10
I / II	26	20
II	159	26
II / III	252	38
III	299	25

Current pipeline

NP pipeline (March 2016)
Number of trials across NP conditions^



- NP assets typically stall after PhII due to the difficulty of showing efficacy in NP
- Of the 223 trials, 27 are being trialled in 2 NP conditions and 5 are being trialled in all 3 conditions
- Common novel MoAs in PhIII include
  - NGF antagonists
  - 5HT Modulators
  - GABA agonists
- 24 assets in development are biologics

- Due to diverse aetiology and heterogeneity of underlying pathophysiology, industry commentators do not expect current late phase studies to yield any assets with robust enough efficacy to alter SoC across NP conditions
  - the one asset in registration is Endo's buccal buprenorphine, which is expected to be similar to other, currently-available opioids

Note: * PRO: Patient reported outcome; ADL: Activities of daily living; SF-36: Short form 36 questionnaire. ** Data based on clinicaltrials.gov pull for neuropathic pain interventional completed trials with results ^ Identified NP conditions are broad NP, diabetic neuropathy, post-herpetic neuralgia .

Source: clinicaltrials.gov; Fibromyalgia.com; Pharmaprojects; Dworkin et al (2010) MayoClinic Proceedings; Datamonitor

What is the ideal TPP for a NP asset?

A TPP for the ideal neuropathic pain asset	
Value proposition	• A targeted therapy for NP disorders with higher response rates and efficacy over currently available therapies
Indication and usage	• Indicated for use across NP conditions, having successfully demonstrated efficacy in 3 or more conditions including general NP, diabetic neuropathy and post herpetic neuralgia • Targeted to identifiable patient subgroups to reliably predict responders
Administration and dosing	• Once-daily oral administration is ideal
Efficacy	• NNT* lower than Lyrica (2.9) • Improved duration of pain relief vs. Lyrica • Disease-modifying where possible
Safety and tolerability	• NNH* not worse than currently available treatments (3.7 for minor side effects with Lyrica) • Limited drug-drug interactions
Pricing and reimbursement	• Although generic pregabalin will be available in 2018, there is potential to match current branded product pricing with a strongly differentiated and efficacious product

Note: * NNT: number needed to treat, i.e. number of patients who would have to take the drug for one patient to have pain relief of 50% or more. NNH: number needed to harm, i.e. number of patients who would have to take the drug for one patient to report a harmful side effect.

Source: Moore et al Cochrane Database Syst Rev, 2009/3

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

DRAFT

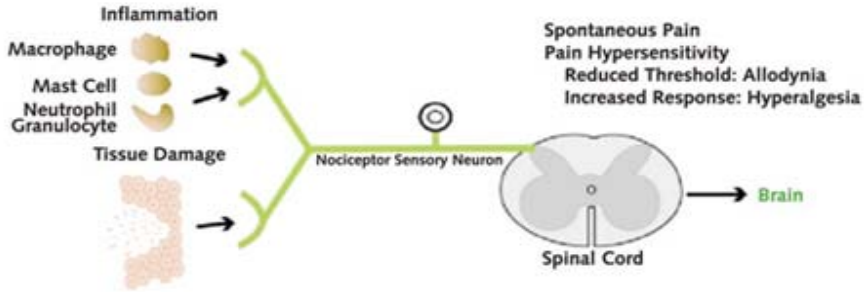
Despite the large potential patient pool in NAMSP, it may be challenging to identify a therapy that meets unmet needs in the mature, genericised market

Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• Treatments are efficacious but poorly tolerated, with GI and CV side effects from NSAIDs and COX-2 inhibitors, as well as abuse potential and side effects of opioids. Currently no disease modifying treatment
Validation of disease & treatment		20%	• Well-understood aetiology for lower back pain. Precise aetiology is not well-understood in OA, but recent advances have provided some validation for new drug targets, e.g. NGF
Competitive intensity		10%	• Highly genericised treatment algorithm with well-established NSAID and opioid treatment options make this a mature and competitive market. Few pipeline assets with potential to change the SoC
Market opportunity		10%	• Large patient population of 330m for OA and CLBP, with patient numbers forecast to increase with rising prevalence of obesity and other lifestyle factors
Probability of clinical trial success		10%	• Endpoints are relatively standardised across NAMSP indications. Most products receiving indications in CLBP or OA in recent years have been reformulations of NSAIDs, COX-2 inhibitors or opioid combos
Overall attractiveness			• Despite ***high prevalence and unmet needs*** in treatment, a new product would have to show significant improvement in safety and/or efficacy or disease modifying potential in order to justify value in a competitive, genericised market

NAMSP includes the common conditions of osteoarthritis and chronic lower back pain, which both have large, and growing, patient numbers

Indication overview

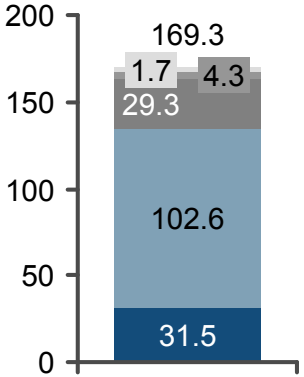
Schematic mechanism of chronic nociceptive pain



- Non-autoimmune musculoskeletal pain (NAMSP), as covered here, is chronic, nociceptive, somatic musculoskeletal pain not associated with auto inflammation
  - the most common NAMSP conditions include osteoarthritis (OA) and chronic lower back pain (CLBP)
  - paediatric NAMSP is not included in this analysis due to its more acute nature and doctors' limited willingness to treat
  - cancer pain arising from skeletal metastasis is analysed as its own category and not included in this NAMSP analysis
- Chronic pain represents a continuum, but can be divided into mild, moderate and severe depending on score on comparative pain scale
- The duration of pain required to be considered chronic is long lasting, typically considered to be at least 60 days to 6 months

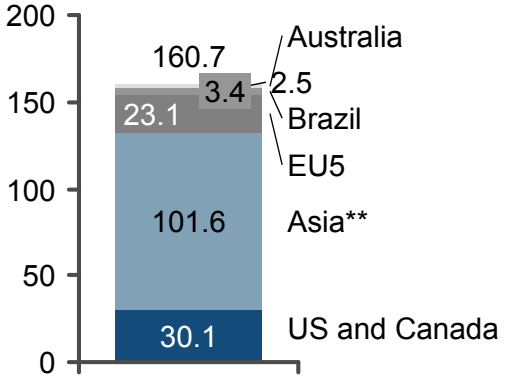
Epidemiology

Prevalence of OA
Millions of patients*



Prevalence of CLBP
Millions of patients*

INDICATIVE



- NAMSP conditions are highly prevalent, impacting the global adult population at relatively consistent prevalence rates (age standardised point prevalence of 7-13%) across studies, geographies and classifications of disease
- OA has a significantly increased prevalence in adults aged >44, affecting between 30-50% of older adults across geographies, with OA of the knee being the most prevalent
- CLBP has an estimated life-time incidence rate of between 70-85% in the developed world, and typically resolves after 6 months
- High growth rates are predicted for NAMSP due to increases in global obesity rates

Note: * Estimated based on population above 15 yo. ** Includes Malaysia, China, Singapore, Philippines, South Korea. ^ ACR: American College of Rheumatology
Source: WHO; CDC; Johannes et al 2010

The current treatment paradigm involves using progressively strong analgesics until surgery, as no disease modifying agents are available

Disease aetiology / pathophysiology

- Risk factors for developing NAMSP are well-defined and consistent across conditions:
  - older age
  - female gender
  - obese
  - lack of physical activity
  - occupational hazards
- CLBP typically arises from mechanical injury, diseases or stresses to the lower back
- OA is characterised by a degradation of cartilage matrix in joints. Although the precise aetiology is idiopathic in most cases, knowledge of disease mechanisms has increased in recent years, including:
  - interplay of key joint components and mechanisms that lead to degradation
  - damaging influencers on hylagine cartilage that can cause degradation

Current treatment paradigm

Typically later lines of therapy

Non pharmacological

- Physical therapy, patient education, lifestyle changes

Non-opioid analgesics

- Acetaminophen / paracetamol
- Topical NSAIDs, lidocaine capsaicin patches for OA

Non-opioid analgesics

- Oral NSAIDs/COX-2 inhibitor
- +/- Proton pump inhibitor

Opioid analgesics/ intra-articular injections

- Hyaluronic acid/corticosteroid injections into affected joint
- Progressively stronger opioid use
- Antidepressants e.g. Cymbalta

Surgery

- Typical surgeries
  - Joint/spinal fusion
  - Joint replacement/artificial discs
  - Osteotomy

- Paracetamol is the first line treatment of choice and, in OA patients, is used in conjunction with topical analgesics at the affected joint
- As patients progress, systemic NSAID medications and COX-2 inhibitors are used, initially alone, then in combination
- Corticosteroid injection into the affected site may be used after systemic NSAIDs, though this is more common in the US than EU5
- Cymbalta is also used as a third-line option in the U.S. and is sometimes used off-label in the EU
- Opioids are typically given to uncontrolled patients, patients awaiting surgery, or those who are not candidates for surgery
- 50% of OA patients progress to the need for surgery, typically within a median timeframe of 13 years
- CLBP patients with pain persisting over 1 year may be referred to surgery. More common in the US

Source: NICE

There is a clear need for disease-modifying agents to speed CLBP recovery and reduce the need for OA surgery, along with reduced side effects over current analgesics

Currently marketed treatments

- 90% of the spend on treatment is on diagnosis, hospitalisations, and surgeries, with minimal value arising from pharmaceuticals
- The market is highly genericised; there are few remaining patent-protected drugs that are used to treat NAMSP
  - reformulations of NSAIDs
  - reformulations and combinations of COX-2 inhibitors
  - opioid combinations
- Paracetamol and NSAIDs drive the majority of the volume in NAMSP
- Branded products generally have global sales of <$100m USD in OA and CLBP, with limited forecast growth

Key unmet needs

- NAMSP is a huge burden to payors and health systems, and there is a clear need for **disease-modifying therapy, enabling quicker recovery and preventing surgery**
  - the wide prevalence, chronic and debilitating nature of NAMSP has a large economic impact on society at large; estimates from a review of HEOR data suggest back pain alone accounts for as much as 1.5% of a nation's GDP
  - **increasing volumes of surgeries are performed** in OA as surgeons become more comfortable, dramatically increasing costs
- Physician concerns are typical of indications in which there is a **high level of opioid use**: addiction, GI and CNS side effects and potential for abuse
  - the GI side effects of NSAIDs and lack of adherence to GI protective medicines compound the problem
- Physicians are also concerned about the side effects of other common therapies, including the **CV side effects of COX-2 inhibitors** and **CV/CNS side effects of antidepressants**
- Physicians have unmet needs with **injections** as well, citing them as **too invasive and too short acting**

Source: EvaluatePharma; WHO; Cross et al 2014 BMJ; Laufer 2004 Rheumatology; FDA

DRAFT

The NAMSP pipeline is 50% novel MoAs that could reduce side effects over SoC, but are unlikely to have a disease-modifying impact

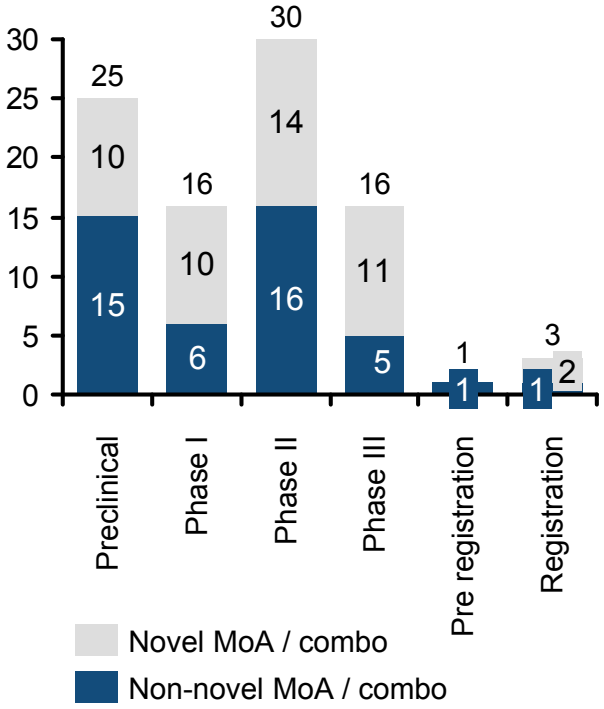
Typical clinical trial design, timing, size

- CLBP primary endpoints used are typically subjective, related primarily to the degree of pain and disability, and use validated patient-reported outcomes measures such as:
  - visual analogue scales (VAS)
  - disability index measures
- OA endpoints are somewhat more established, with the WOMAC LK* scale being the widest used patient reported measure
- OA trials also included more objective endpoints such as physical function tests on the affected joints
- The only approvals since Cymbalta (2010) have been reformulations, as there are few novel products in development

Phase**	Avg enrolment	Avg length (mo)
I	39	17
I / II	53	24
II	114	27
II / III	125	32
III	454	19

Current pipeline

NAMSP pipeline (February 2015)
Assets across trial phases



- 50% of products for both OA and CLBP are novel MoAs
- There is a high degree of overlap between conditions, with 30% of assets in trials for OA also in trials for CLBP
- Novel registration assets are new combinations, e.g. a mu/kappa opioid and a combination corticosteroid for direct injection in affected joints
- Novel MoAs in PhIII include
  - NGF antagonists, by Regeneron
  - novel opioid combos, by Endo International
  - ORL-1 agonist, by Grunenthal
  - novel corticosteroid combination, by Carbylan Theraputics

- Current pipeline assets are not disease-modifying; however, some novel non-opioid analgesics (e.g. NGF antagonists) may have reduced side effects over current SoC

Note: * WOMAC K: Western Ontario and McMaster Universities Osteoarthritis index likert scale. ** Data based on clinicaltrials.gov pull for averages of OA.
Source: clinicaltrials.gov; Pharmaprojects; Business monitor

What is the ideal TPP for a NAMSP asset?

A TPP for the ideal NAMSP asset	
Value proposition	• Disease-modifying treatment for NAMSP that ultimately prevents or delays time to surgery • A significant improvement in efficacy and tolerability vs. current treatments
Indication and usage	• Indicated for use in OA and CLBP • Used over the long term to modify the course of disease
Administration and dosing	• Once-daily oral administration or topical around affected area • Not injected
Efficacy	• Improved efficacy in pain relief over current SoC • Identified subgroups that are likely responders
Safety and tolerability	• Side effect profile better than NSAIDs (GI) and COX-2 inhibitors (CV) in long term use
Pricing and reimbursement	• Must demonstrate clear value over generic referent products in order to command a price premium, which may be based on generic prices

Source: Moore et al Cochrane Database Syst Rev, 2009/3

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

DRAFT

The pain market in autoimmune joint disease offers limited opportunity, though there is a moderate need for higher tolerability and efficacy than currently-available treatments

Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• Current treatments, such as NSAIDs and selective COX inhibitors, offer moderate pain relief, but are associated with gastrointestinal side effects
Validation of disease & treatment		20%	• Pain is multifactorial and pain treatments are non-specific to auto-immune pathology. The majority of the pipeline is also non-specific, targeting undefined arthritic pain
Competitive intensity		10%	• Crowded market with NSAIDs and other analgesics, available in topical and oral formulations, albeit that they offer non-targeted pain relief. DMARDs prevent pain and offer pain relief, thus presenting indirect competition to analgesics
Market opportunity		10%	• The overall diagnosed population for RA, the most prevalent auto-immune arthritic disease, is 4.7m across Mundi/Purdue territories, with patients requiring pain relief both during remission and disease flares
Probability of clinical trial success		10%	• The clinical endpoints are well-defined and commonly-used metrics such as ACR and DAS28^ are used in most studies*
Overall attractiveness			• Despite pain relief being difficult to achieve in auto-immune conditions, such as RA, targeted development of pain relief is likely to be difficult due to the lack of scientific validation, whilst the market opportunity is limited by generics and by indirect competition from DMARDs

Note: ^ American College of Rheumatology and Disease Activity Score; * Research focused on RA, the most prevalent auto-immune arthritic condition

DRAFT

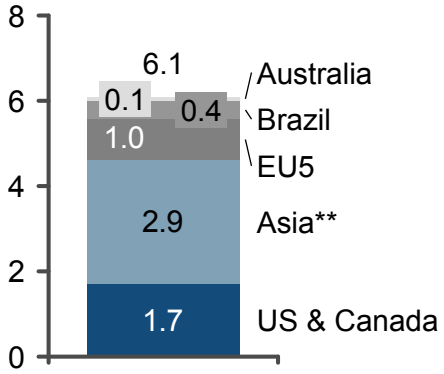
RA is the most prevalent autoimmune joint disease, with 4.7m patients diagnosed in Mundi/Purdue territories; pain is a prominent feature throughout the disease

Indication overview

- Autoimmune disorders occur when the body's immune system attacks and destroys healthy tissue
- Joints and muscle are common sites of autoimmune inflammation, which can lead to pain that persists even beyond disease flares
- Common autoimmune conditions that affect the musculoskeletal system include rheumatoid arthritis, polymyalgia rheumatica, psoriatic arthritis, ankylosing spondylitis, Sjogren's, systemic lupus erythromatosus and systemic sclerosis
- This analysis focuses on rheumatoid arthritis (RA), as pain control is a significant unmet need in RA and RA offers the largest market opportunity of autoimmune conditions as the most prevalent and well-characterised autoimmune arthritis
  - RA is characterised by joint inflammation that leads to joint deformity across multiple joints

Epidemiology

Prevalence of RA (2015)
Millions of patients*



INDICATIVE

- The prevalence of RA across Mundi/Purdue geographies varies between 0.2% in Asia and 0.6% in the U.S. due to regional variation in behavioural factors, climate, environmental exposures, RA diagnosis and genetic profile
- The total addressable population in Mundi/Purdue territories is 6.1m
- The diagnosis and treatment rates of RA are high, with a reported diagnosis rate of 75-80% and treatment rate 85-90% in the U.S. and Europe
- The overall diagnosed population is estimated at 4.7m*
- Pain affects patients with active disease during flares, and up to 95% of patients experience at least one flare per year
- Even during remission 10% of patients experience pain

Note: * U.S. and EU5 diagnosis rate has been applied to all territories ** Includes Malaysia, China, Singapore, Philippines, South Korea.
Source: American Medical Association's journal of internal medicine; The Journal of Rheumatology; Drugs Journal

The aetiology of RA pain is partly understood, but the role of different targets remains unclear, so RA pain is treated with non-RA-specific analgesics and DMARDs

Disease aetiology / pathophysiology

- The precise aetiology and pathogenesis of RA pain are partly understood
- Pain in RA is mediated through multiple mechanisms and pathways thus offering a large number of targets; however, their individual contribution to pain is unclear
- Peripheral nociceptors are triggered by mechanical stimuli (e.g. weight bearing) and by a number of chemical halogens, such as TrpV1
- A number of cytokines, growth factors, and interleukins enhance peripheral stimulation by further sensitising the nerves
  - commonly used NSAIDs and steroids target the release of cytokines and other inflammatory compounds to reduce pain
- Central processing of pain appears to be augmented in RA, reducing pain threshold and causing mechanical pain to be felt beyond the immediately affected area
- Furthermore, the psychological stress associated with the disease is thought to further exacerbate the perception of pain
- Understanding of the pathology has guided the preferential choice of NSAIDs; however, RA targets, such as TrpV1, have failed to demonstrate clinical benefit and their roles remain unclear

Current treatment paradigm

RA pain SoC

Mild

Pharmacologic

- Pro re nata OTC analgesics (e.g. paracetamol or ibuprofen)
- Prescription NSAIDs and steroids

Moderate

Pharmacologic

- Long-term treatment with DMARDs
- Pro re nata or long-term NSAIDs
- Weak opioids

Severe

Pharmacologic

- Long-term treatment with DMARDs
- Long-term NSAIDs and oral steroids
- Steroid injections
- Strong opioids

Other

- Apply ice packs on inflamed joint or warm compress on stiff joints
- Regular exercise may improve joint pain
- Counselling and reducing stress may alter pain perception
- Physiotherapy may reduce mechanical stress on joints

- Pain relief in RA is an integral part of the management plan
- Pain is managed with agents that are not specific to RA but have anti-inflammatory properties, such as NSAIDs
- Opioids are used when pain is not adequately controlled despite the use of NSAIDs, as per the WHO pain ladder
- DMARDs control disease progression and reduce pain in moderate and severe disease

Source: Nature Reviews Rheumatology

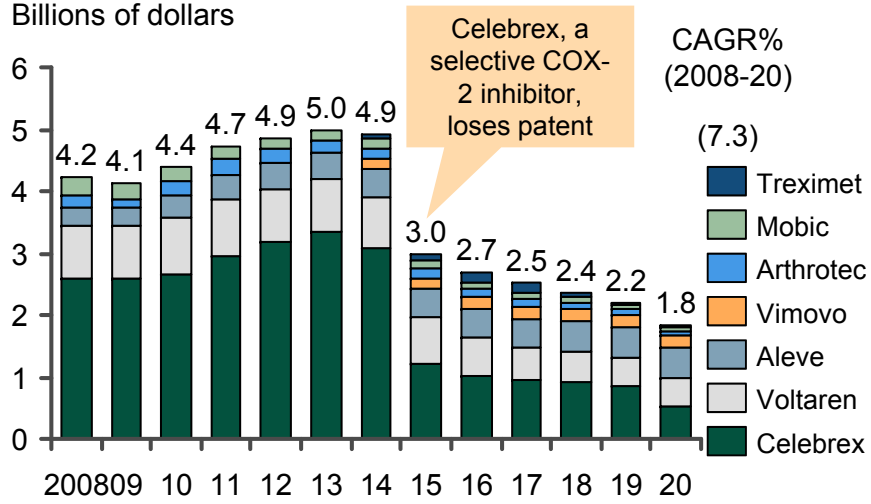
DRAFT

Improved tolerability and efficacy of analgesics in RA is an identified unmet need, but development of better DMARDs may reduce incidence of pain within RA

Currently marketed treatments

Global market for RA pain drugs (2008-20)*

Billions of dollars



- Following the patent loss of the blockbuster drug celecoxib (Celebrex) in 2014, a selective COX-2 inhibitor, the total value of the market of branded NSAIDs decreased significantly
- Generic NSAIDs are widely available both as OTC and prescription products applying constant pressure on the market
- The pain pipeline for RA is small, with the majority of products reformulations of already launched drugs, therefore the prices of NSAIDs and opioids are expected to remain the same or decrease over time

Key unmet needs

- DMARDs are moderately effective in controlling RA flares and disease progression; however, efficacy varies between patients
- The **efficacy of analgesic anti-inflammatory agents in RA is moderate** with a NNT^ around 8 and 33% of patients showing ACR 20** improvement of their pain at 12 weeks
  - NSAIDs, including selective COX-2 inhibitors, have demonstrated similar efficacy
- Regular administration of NSAIDs is **associated with increased risk of ulceration of the gastrointestinal tract**, which may limit their usage
  - patients are frequently co-administered protein pump inhibitors to protect from excess acid secretion
  - patients at high risk of ulceration are administered NSAIDs with extreme caution
  - NSAIDs are more likely to cause gastrointestinal adverse events than celecoxib, but both MoAs carry increased risk
- Current treatments **fail in addressing the multifactorial nature of pain in RA**, including central and peripheral sensitisation
  - pain remains the most common complaint of patients with RA

Note: * Sales represent sales of top 7 NSAIDs as sales of non-branded products are underreported, ^NNT: number needed to treat; **ACR 20:American College of Rheumatology score to state the patient has at least 20% fewer tender joints and at least 20% fewer swollen joints.

Source: Arthritis Research and Therapy; BMJ; Clinical Medicine & Research; EvaluatePharma; FDA; Medicine.ox.a~uk; Open Journal of Rheumatology and Autoimmune Disease

DRAFT

The pipeline primarily targets broad arthritic pain, with only four assets specific to RA pain. None of these are expected to impact the SoC in RA pain

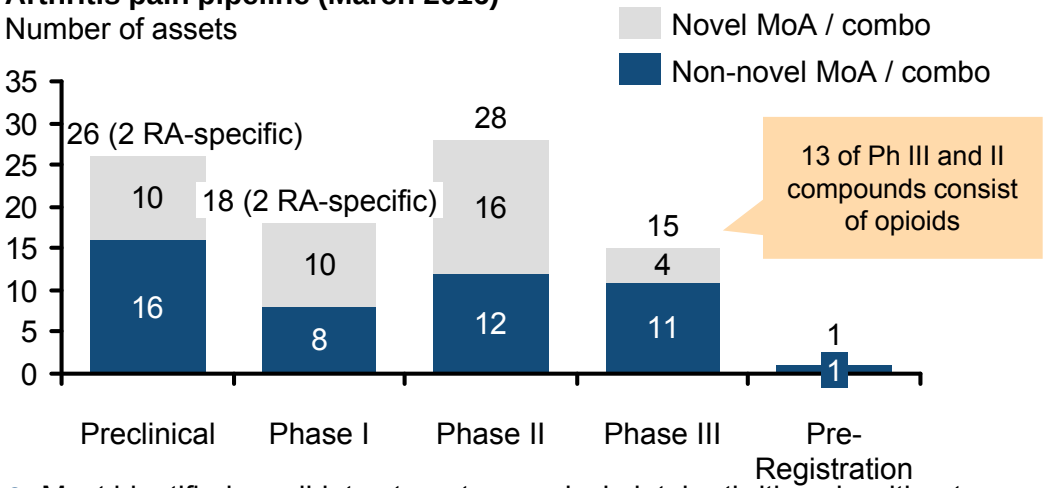
Typical clinical trial design, timing, size

- The majority of clinical trials in RA utilize DMARDs to relieve inflammation and reduce pain
- The use of NSAIDs, including selective COX-2 inhibitors, as analgesic agents in clinical trials is less frequent; however, the clinical points appear consistent
  - agents are tested in both RA and OA, against placebo drugs and measurements are reflected against baseline activity
  - the safety and the tolerability are assessed with emphasis on patients who experience at least one adverse event or discontinue medication
  - pain intensity is measured with the Visual Analog Scale or with more holistic RA severity scoring systems such as the ACR or DAS28^

Phase	Avg enrolment	Avg length (mo)
I	42	20
I / II	50	21
II	165	27
II / III	205	31
III	520	38

Current pipeline

Arthritis pain pipeline (March 2016)



- Most identified candidates target musculoskeletal arthritic pain without specifically pursuing an RA indication
  - PhII and PhIII trials for these therapies are primarily recruiting patients with osteoarthritis rather than RA
- The pipeline for RA-pain-specific treatments consists of four drugs, two in preclinical and two in Ph I
- Candidates identified include ibuprofen and celecoxib reformulations utilising novel RoAs (e.g. transdermal application)
- The single novel agent for RA pain is a Ph II VAP-1 antagonist, licensed to Roche, trialled for its capacity to control RA flares and eliminate joint pain in RA through modifying disease activity. It is not expected to impact the use of analgesics in the RA SoC unless it outperforms currently-available DMARDs

Note: ^ American College of Rheumatology and Disease Activity Score.
Source: clinicaltrials.gov; Pharmaprojects

What is the ideal TPP for an autoimmune musculoskeletal disease pain asset?

A TPP for the ideal autoimmune joint disease pain asset	
Value proposition	• A targeted therapy for autoimmune joint pain, which addresses the multifactorial nature of pain and demonstrates higher efficacy and higher tolerability than non-specific NSAIDs
Indication and usage	• Indicated for use in patients with a diagnosed autoimmune condition which causes joint pain • To be used to alleviate pain during flares of disease and during disease remission
Administration and dosing	• Pro re nata oral or topical administration
Efficacy	• NNT* lower than NSAIDs, for example less than 8 in RA • Reduction of stress and depression in line with pain reduction in patients
Safety and tolerability	• Higher tolerability than selective COX-2 inhibitors with reduced incidence of gastrointestinal side effects, such as peptic ulcers and GI pain
Pricing and reimbursement	• Pricing of the drug could be higher than celecoxib if improved tolerability is demonstrated with reduction of the incidence of peptic ulcers and/or higher efficacy is achieved

Note: * NNT: number needed to treat.
Source: Moore et al Cochrane Database Syst Rev, 2009/3

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

Cancer pain

DRAFT

There is moderate unmet need for a non-opioid alternative to treat cancer pain, as currently-available opioids are efficacious when used appropriately

Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• As currently-available therapies for cancer pain are largely effective in addressing the pain, the unmet need is related to developing therapies with fewer side effects and less abuse potential
Validation of disease & treatment		20%	• Aetiology and pathophysiology are relatively well-understood and the pain can be neuropathic or nociceptive. Current treatments, especially strong opioids, are effective in addressing cancer pain, if it is properly assessed
Competitive intensity		10%	• The market is largely generic with significant off-label use, but there is room for more targeted treatments (e.g. for CIPN) and non-opioid therapies. The cancer pain pipeline contains mostly non-novel non-opioids, while the CIPN pipeline contains several novel MoAs; both may reduce the degree of unmet need
Market opportunity		10%	• 3m patients affected across MDP / Purdue geographies every year. Market expected to grow at 9% p.a. driven by unmet needs and challenged by off-label use.
Probability of clinical trial success		10%	• A history of approvals for breakthrough cancer pain. No history of approvals for CIPN, for which trial endpoints are more complex due to the neuropathic nature of the pain
Overall attractiveness			• ***Moderate unmet need.*** The highest unmet need in cancer pain is in having the pain properly assessed and treated rather than developing more efficacious treatments. However, there could be an opportunity to develop more targeted treatments with fewer side effects and lower abuse potential

Cancer pain

DRAFT

About half of cancer patients experience some degree of pain, which is inadequately treated in 30% of patients who do not receive a suitable pain therapy

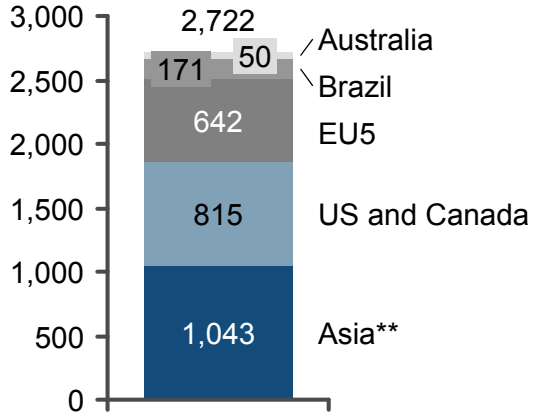
Indication overview

- Cancer pain is experienced in all phases of cancer
- More than half of advanced cancer patients experience moderate-to-severe pain
- The cause may be structural changes to surrounding tissues caused by a growing tumour (75% of cases) or treatments and diagnostic procedures (25% of cases)
- Cancer pain can be chronic or acute and may have neuropathic or nociceptive origin
- Cancer pain is not adequately treated in 30% of patients, who do not receive sufficient treatment for their pain intensity
- Often cancer pain is also associated with psycho-social distress, which can significantly reduce the patient's QoL

Epidemiology

Prevalence of cancer pain (2015)
Thousands of patients*

INDICATIVE



Prevalence likely to increase with increasing cancer prevalence due to ageing population

- Cancer pain is assessed using a visual analogue scale (VAS), a verbal rating scale (VRS) and a numerical rating scale (NRS)
- The following prevalence rates for cancer pain have been reported in a meta-study of >50 publications across geographies
  - 33% for patients after curative treatment
  - 59% for patients on anti-cancer treatment
  - 64% for patients with advanced, metastatic or terminal cancer
  - 53% for patients with all stages of cancer

Note: * All cancers excluding non-melanoma skin cancer. Adult patients only. Pain prevalence rates estimated for patient populations with mean age of 60 years old. ** Includes Malaysia, China, Singapore, Philippines, South Korea.
Source: Globocan; Greco *et* al. (2014) Journal of Clinical Oncology; Ripamoti *et* al. (2011) Annals of Oncology; van den Beuken-van Everdingen *et* al. (2007) Annals of Oncology

Cancer pain

DRAFT

There is a well-established and effective treatment paradigm for cancer pain, whose aetiology and physiology are relatively well-understood

Disease aetiology / pathophysiology

- The aetiology of cancer pain is varied but usually possible to establish
- Neuropathic cancer pain usually stems from the tumour inflicting damage on the nerve by compression, transection, infiltration, ischemia, or metabolic injury
- A sub-type of neuropathic cancer pain, CIPN*, is caused by chemotherapy damaging peripheral nerves
- Nociceptive cancer pain may be the result of a surgery aiming to treat the cancer or of tumour metastases
- For example, somatic nociceptive cancer pain can be caused by a radiation-related skin burn, while visceral pain may be the result of a liver enlarged by the cancer
- Therefore, understanding of the mechanisms of cancer pain is evolving with understanding of the pathophysiology of neuropathic and nociceptive pain

Some specific types of cancer pain, such as bone pain, are treated with specific drugs, such as Clasteon (clodronate disodium)

Current treatment paradigm

Mild pain SoC

Non-opioid analgesics
- Acetaminophen / paracetamol
- NSAIDs and COX-2 selective inhibitors

Mild-moderate pain SoC

Non-opioid analgesics
- Acetaminophen
- Aspirin
- NSAID

Weak opioid analgesics
- Codeine
- Tramadol
- Dihydrocodeine

Moderate-severe pain SoC

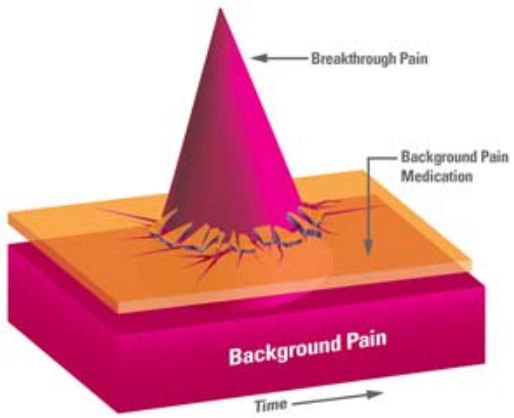
Strong opioid analgesics
- Morphine
- Methadone
- Oxycodone
- Hydromorphone
- Fentanyl
- Alfentanyl
- Buprenorphine
- Heroin
- Levorphanol
- Oxymorphone

- The WHO three-step analgesic ladder is used for cancer pain management
- With currently available medications, the associated pain can nearly always be treated to the patient's satisfaction, though some doctors may not adequately treat cancer pain
- Opioids are often combined with non-opioids to achieve maximum relief
  - among strong opioids, oral morphine and fentanyl are typically the opioids of choice
  - Oxycontin and buprenorphine are other popular strong opioids
- Oral RoA is usually advocated, but for urgent relief more potent SQ and IV opioids are used
- For neuropathic cancer pain, non-opioids and opioids may be combined with TCAs or anti-convulsants
- Patients nearing death who are refractory to treatment can be given sedatives, including neuroleptics, benzodiazepines, barbiturates and propofol

Note: * CIPN, chemotherapy-induced peripheral neuropathy.
Source: CRUK; Ripamoti *et* al. (2011) Annals of Oncology; von Gunten (2011) Journal of Pediatric Hematological Oncology; WHO analgesic ladder

Within cancer pain, breakthrough pain and CIPN are common sub-indications for which specific treatments may be considered

Breakthrough cancer pain



- Breakthrough pain is acute pain that is not alleviated by the patient's pain therapy
- Cancer pain is typically well-controlled with chronic therapy but bouts of severe pain may "break through"
- >20% of cancer patients are affected by breakthrough cancer pain
- Management of breakthrough pain typically entails intensive opioid use with fentanyl being one of the more commonly used opioids
- A number of drugs have been approved for breakthrough cancer pain, including Actiq & Fentora (Teva), Abstral & Lazanda (ProStrakan) and Onsolis (BioDelivery Sciences)

Chemotherapy-induced peripheral neuropathy

- 30-40% of patients on chemotherapy are thought to develop CIPN due to chemotherapy-induced damage to their peripheral nerves
- Platinum drugs, taxanes, epothilones, plant alkaloids, Thalomid/Revlimid, Velcade/Kyprolis, Halaven are among the drugs more likely to cause CIPN
- CIPN is characterised by acute or chronic pain, tingling, numbness, temperature sensitivity, et~
- Symptoms usually start in feet and hands and move to legs and arms
- CIPN treatment is focused on relieving the associated pain
- Common pain relief strategies include patches and creams with numbing agents (lidocaine, capsaicin), anti-depressants and anti-seizure drugs, and opioids when the pain is severe
- Currently, therapies for CIPN-associated pain largely overlap with those for cancer pain and other neurological conditions
- There are no therapies specifically approved for CIPN, but some agents, such as glutathione, calcium and magnesium, have shown early promise of helping prevent CIPN

Source: Cancer.org; Medscape; WebMD

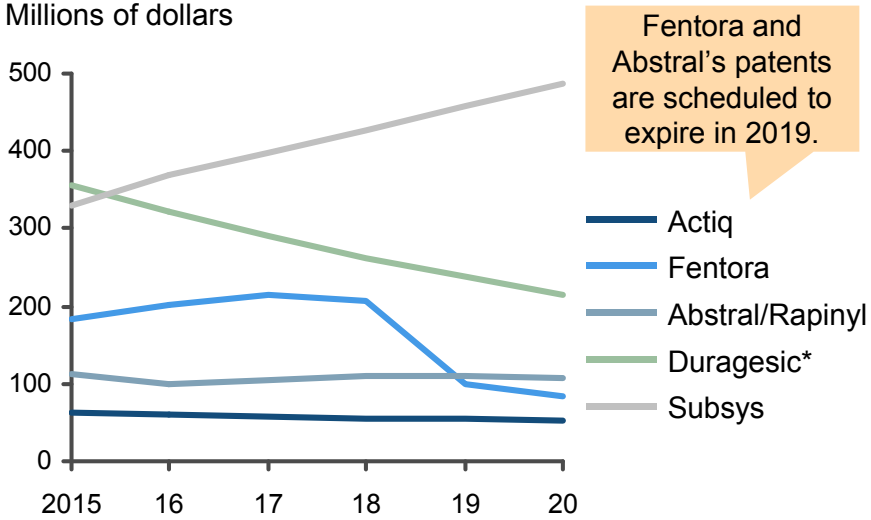
DRAFT

The cancer pain market is expected to grow, driven by launches of novel therapies that combat unmet needs, such as undesirable side effects

Currently marketed treatments

Projected sales for key branded products (2015-20)

Millions of dollars



- In 2013, 70% of volume sales in the cancer pain market in Europe were generics, 90% were oral formulations and >50% were strong opioids
- Fentanyl dominated the value sales, while paracetamol dominated the volume sales
- Currently the cancer pain market is the largest pain market segment, dominated by fentanyl formulations and oral morphine products, and is expected to continue to grow
- Growth is likely to be driven by new product launches, such as the recently launched Subsys

Key unmet needs

- Opioids are a common therapy for cancer pain, therefore managing moderate-to-severe pain with **minimal side effects and addiction** is a key unmet need
  - >50% of patients with advanced cancer will need strong opioids, whose use is often accompanied by severe side effects, such as **nausea and constipation**
  - the **risk of opioid addiction is a more moderate unmet need** for cancer pain patients, given that many patients have a poor prognosis
- Another unmet need is the **treatment of complex cancer pain**, i.e. drugs that can address both nociceptive and neuropathic cancer pain components
- **Improving the rates of cancer pain under-treatment** is also necessary as >30% of patients do not receive pain medication proportional to their pain intensity
  - reasons may include patients' reluctance to report pain or physicians' lack of experience with pain management
  - care is less optimal in the developing world, where cancer pain may not be controlled in 50% of patients

Note: *Not cancer pain-specifi~
Source: BusinessWire; Greco *et* al. (2014) Journal of Clinical Oncology; Management (IMS); Research and Markets; TechNavio

DRAFT

The cancer pain pipeline contains a number of novel non-opioids, such as anti-NGF agents and cannabinoids, that are expected to reduce the need for non-opioid options

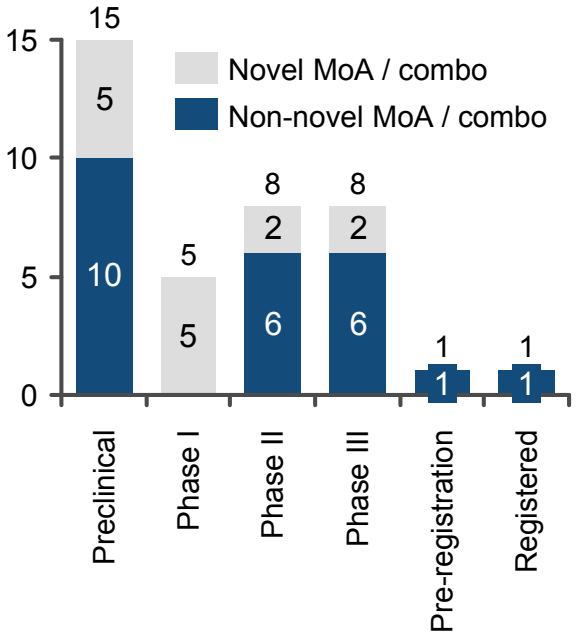
Typical clinical trial design, timing, size

- Primary efficacy endpoints in late stage cancer clinical trials usually include measurements of change in pain intensity from baseline
- There are a number of well-established trial endpoints, with the VAS used more frequently than the NRS or VRS*
- Typically, drugs that have sought and been successful in gaining regulatory approval for cancer pain have been reformulations of opioids, such as fentanyl and morphine
- Drugs for specific kinds of cancer pain, such as Clasteon (clodronate disodium) for bone pain, have also sought and received approval for narrower cancer pain indications

Phase	Avg enrolment	Avg length (mo)
I	53	45
I / II	40	32
II	103	34
II / III	189	29
III	207	42

Cancer pain pipeline

Cancer pain pipeline (March 2016)
Number of assets



This analysis includes therapies in development for breakthrough pain but not CIPN

- 65% of the pipeline assets for cancer pain are non-opioids, which will likely reduce the unmet need
- Non-opioid Phase II assets:
  - Bupizenge, a lozenge of bupivacaine by Moberg Pharma
  - INT-0028, CR dronabinol, by IntelGenx
  - fulranumab, an anti-NGF MAb by Takeda and J&J
  - Rhenium-188-HEDP, a short nuclide by Jiangsu LaiTai Biotechnology Co. for pain from metastatic bone cancer
- Non-opioid Phase III assets:
  - an NSAID patch by Hisamitsu
  - tanezumab, an anti-NGF MAb by Pfizer
  - Tectin (tetrodotoxin-based) by Wex Pharmaceuticals
- The late stage opioid pipeline for cancer pain includes formulations of fentanyl (Oneduro by J&J, NKQ-01 by Kyukyu Pharma and Nippon), a nanotab formulation of sufentanil (ARX-02 by AcelRx), cebranopadol (by Gruenenthal) and tilidine hydrochloride (a synthetic narcotic by Aoxing Pharma)

Note: * VAS: visual analogue scale; VRS: verbal rating scale; NRS: numerical rating scale.
Source: clinicaltrials.gov, Pharmaprojects

DRAFT

In addition to the broader cancer pain pipeline, several therapies are pursuing a specific indication for CIPN

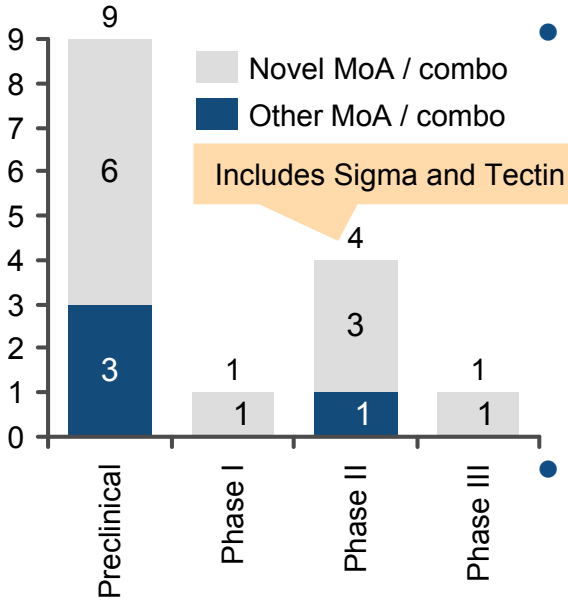
CIPN clinical trial design, timing, size

- Currently, there are no drugs approved for CIPN
- Most agents used to treat CIPN have been studied in patients with PHN and PDN^
- Given the range of symptoms, reliable efficacy endpoints to measure the treatment, prevention, and mitigation of CIPN have yet to be established
- Promising CIPN measures are thought to be:
  - the Functional Assessment of Cancer-Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX)
  - an abbreviated version of the Total Neuropathy Score (TNS)
  - the EORTC^ Quality of Life Questionnaire-CIPN twenty-item scale (QLQ-CIPN20)

Phase	Avg enrolment	Avg length (mo)
I**	35	10
II	55	22
III	173	57

CIPN pipeline

CIPN pipeline (March 2016)
Number of assets



- Most "other" MoA/ combo assets in development for CIPN have unidentified pharmacological activity
- Late stage novel MoA / MoA combination assets include:
  - EpiCept NP-1, a topical cream combination of amitriptyline and ketamine by Immune Pharmaceuticals, in Phase III
  - EMA-401, an angiotensin II type 2 receptor antagonist by Spinifex Pharmaceuticals, in Phase II
  - KRN-5500, a spicamycin derivative by Midatech, in Phase II
- Earlier stage novel MoA / MoA combination assets include:
  - KP-544, an NGF potentiator, by Krenitsky in Phase I
  - SPI-205 (leteprinim potassium) by Spectrum Pharmaceuticals in Phase I
  - a first-in-class FAAH inhibitor by Advinus in pre-clinical
  - HM-01, a ghrelin receptor agonist 1 by Helsinn in pre-clinical
  - SV-250, a novel CSE* inhibitor by Sova Pharmaceuticals in pre-clinical
- Most assets in development for CIPN are being developed for neuropathic pain in general, and they are not expected to have the efficacy to alter the SoC either in NP or in CIPN

Note: * CSE: cystathionine-gamma-lyase. **Based on 2 trials. ^PHN: post-herpetic neuralgia; PDN: peripheral diabetic neuropathy; EORTC: European Organization of Research and Treatment of Cancer.
Source: Cleeland *et* al. (2010) The Oncologist; clinicaltrials.gov, Pharmaprojects

What is the ideal TPP for a cancer pain asset?

A TPP for the ideal cancer pain asset	
Value proposition	• Reduction of the constipation and nausea associated with opioid use and little abuse potential, although the latter is an unmet need of moderate importance for cancer pain as many patients have poor prognosis
Indication and usage	• Indicated for moderate-to-severe cancer pain • Able to address the multitude of symptoms associated with the complex nature of cancer pain, which involves both neuropathic and nociceptive pain stimuli
Administration and dosing	• Preferably oral RoA, although patches and sprays are also commonly used for cancer pain as depending on the type and stage of disease, some patients may require an alternative RoA • Once daily or less
Efficacy	• Efficacy comparable to currently available strong opioids used for cancer pain management
Safety and tolerability	• Side effects comparable to current non-opioid therapies and improved over opioid-related side effects, such as constipation and nausea
Pricing and reimbursement	• Pricing potential may be limited by the high genericisation of the market, however, there is an opportunity for favourable pricing if the asset is innovative enough, e.g. non-opioid and with a convenient novel RoA

Source: BusinessWire; Cancernetwork.com; Research and Markets; TechNavio

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

Post-operative pain

DRAFT

The POP market could be an attractive opportunity as, although the unmet need is moderate, there are few marketed and pipeline assets able to address all aspects

Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• A need to move away from opioids to avoid side effects and late discharge, though this is being addressed with multimodal analgesia. POP tools with up to 72 hours efficacy and fewer safety and patient mobility issues are needed
Validation of disease & treatment		20%	• Most POP has nociceptive origin and results directly from the surgical insult. Chronic POP is less common
Competitive intensity		10%	• A large proportion of generics (60% value sales and 80% volume sales) on the market. A relatively large pipeline, but novelty is limited to a few assets, of which one or two may impact the SoC
Market opportunity		10%	• 138m inpatient and outpatient surgeries in US and EU5 were performed in 2015. Market expected to grow driven by increasing adoption of long-acting local anaesthetics, such as Exparel.
Probability of clinical trial success		10%	• Development of POP assets requires a number of late stage clinical trials across different surgical settings. However, failure in some settings does not appear to preclude approval for a narrower indication
Overall attractiveness			• ***Moderate unmet need***. Some of the unmet need is likely to be addressed by increasing adoption of multimodal analgesia. A long-lasting analgesic requiring a single application and with efficacy spanning over the first 72 hours post-surgery could be an attractive opportunity in this market

Post-operative pain

DRAFT

140m surgeries are performed in the US and EU5 every year; the effective management of POP can reduce hospital costs and increase patient satisfaction

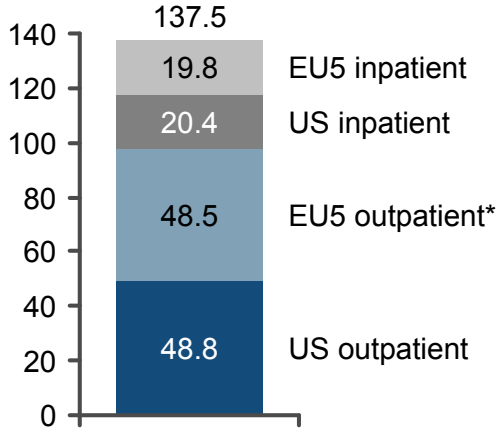
Indication overview

- Post-operative pain (POP) is **typically acute pain** (less often persistent) associated with a surgical procedure
  - following an invasive procedure, patients often experience moderate-to-severe pain for several days
- Acute POP is typically regarded as pain occurring for no more than 7 days following an operation
- Persistent or chronic POP is less common and may result from nerve injury and neuroplastic changes in the CNS induced by severe pain in the first days following surgery
- Effective management of POP has been shown to result in shortened hospital stays, reduced hospital costs, reduced risk of chronic pain and increased patient satisfaction

Epidemiology

Estimate of inpatient and outpatient surgeries in the US and EU5 (2015)

Millions of surgeries



INDICATIVE

Generally, outpatient procedures are expected to grow slightly at the expense of inpatient ones

- Nearly 140M surgeries were performed in the US and EU5 in 2015, with 70% of surgeries being outpatient surgeries
  - data was not readily available for other Mundi/Purdue geographies, but would likely represent a significant additional population
- Following surgery and before discharge, 88% of inpatients experience moderate-to-severe pain
  - 30% experience moderate pain
  - 17% experience severe pain
  - 18% experience extreme pain

Note: * Number of EU5 outpatient surgeries was estimated based on the reported number of EU5 inpatient surgeries and the US proportion of inpatient to outpatient surgeries

Source: Apfelbaum *et* al. (2003) Anesthesia and analgesia; Botti *et* al. (2014) Implementation Science; CDC; Cowen; Medscape; UptoDate; Vadivelu *et* al. (2010) Journal of Biology and Medicine; OECD; WHO

Post-operative pain

DRAFT

POP management has historically relied on opioids; however, there is a growing trend to use multimodal analgesia to reduce general analgesic and opioid use

Disease aetiology / pathophysiology

- POP results from the inflammation caused by tissue trauma or direct nerve injury
  - inflammation may be caused by a surgical incision, dissection, or burns
  - nerve injury can result from nerve transection, stretching, or compression
- Most POP is nociceptive and results from the surgical insult, while neural sensitisation plays an important role in persistent POP

The POP management method used depends on the procedure, pain severity, age, gender, and patient preference

The general aim of POP management is to relieve pain, achieve early mobilisation after surgery, and reduce length of hospital stay

Current treatment paradigm

POP management methods

Regional anaesthesia by nerve block
- Single injection / continuous infusion of local anaesthetics to block nerves in an area (single injection lasts 6-12 hrs)

Epidural local anaesthesia
- Local anaesthetics injected epidurally for short-term (4 hrs) pain relief
- A catheter with local anaesthetics providing a continuous infusion into the epidural space

Incisional local anaesthesia
- A single or continuous infusion of local anaesthetics to an incision site using an infusion pump or elastomeric bag

Intravenous systemic analgesia
- NSAIDs and opioids introduced intravenously, either continuously or when the patient requests

Oral and SQ systemic analgesia
- NSAIDs, aspirin, paracetamol, opioids and others, typically used as add-on to other forms of POP management

- POP has historically been largely managed with systemic opioids
  - typical weak opioids used for POP are codeine, dextropropoxyphene, and tramadol; strong opioids are morphine, fentanyl, and buprenorphine
- There has been a trend from using opioids alone to multimodal analgesia, the local and systemic administration of a mixture of weak and strong opioids and non-opioids
- Multimodal analgesia aims to achieve a synergistic effect, using lower doses of individual analgesics to reduce opioid-related side effects
  - for example, certain adjuvants (e.g., capsaicin, ketamine, gabapentin, pregabalin) are used with opioids to reduce opioid dosing
- In addition, use of non-opioid medications, such as NSAIDs+acetaminophen and local anaesthetics (nerve blocks, tissue infiltration, wound instillation), can prevent use of opioids
- Patient-controlled analgesia (PCA) is a common form of POP management, which is patient-controlled administration of pain medication, usually opioid, post-surgery
- In addition to PCA, local anaesthesia, which relies on non-opioid medications only, has been gaining relevance in POP management with the development of long-acting local anaesthetics and the increasing use of multimodal analgesia

Non-opioid anaesthesia

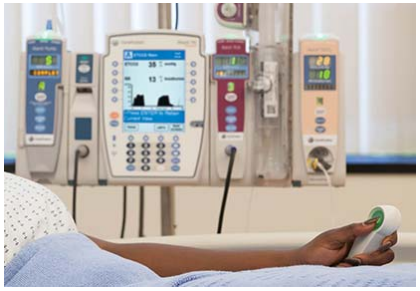
Source: Botti *et* al. (2014) Implementation Science; Cowen; UptoDate; Vadivelu *et* al. (2010) Journal of Biology and Medicine

Post-operative pain

DRAFT

PCA is a common type of POP management, but the importance of non-opioid local anaesthesia in POP management has been growing

Patient-controlled analgesia



- PCA is a POP management option that involves the patient self-administering pain relief medication using a programmable device
  - up to 60% of inpatients who have had surgery are estimated to be given PCA
- PCA allows the patient's treatment regimen to be adjusted and provides immediate relief, potentially improving recovery and allowing for earlier discharge
- PCA has been recognised as an effective POP management tool in terms of both delivery and efficacy as it is able to address moderate-to-severe pain without multiple injections
- PCA has several disadvantages, such as using opioids (usually IV morphine/hydromorphone), restricting patient mobility, and having the potential of programming errors and injection site infections
- Zalviso is a novel PCA option (approved in Europe in 2015), which utilises a sublingual nanotab formulation of sufentanil and aims to address some of the unmet needs for IV PCA

Local anaesthesia

- Local anaesthesia, which relies on non-opioid medications, is injected directly into the wound site or nerve fibre and aims to induce local insensitivity to pain
- Local anaesthetics have been used for pre- and intra-operative pain management for some time due to their high efficacy and include procaine, lidocaine, ropivacaine, and bupivacaine
- They have not been historically regarded as a POP management tool; however, with the development of long-acting local anaesthetics, their importance in POP has been increasing
- The idea is that long-acting local anaesthetics could extend into the POP setting because they slowly release the anaesthetic over time once injected into the chosen site
- Exparel is the first long-acting local anaesthetic on the market and contains bupivacaine, which is slowly released over 72 hrs
- However, its efficacy only lasts about 12 hours, as bupivacaine appears to be deactivated by local inflammation

Source: Cowen

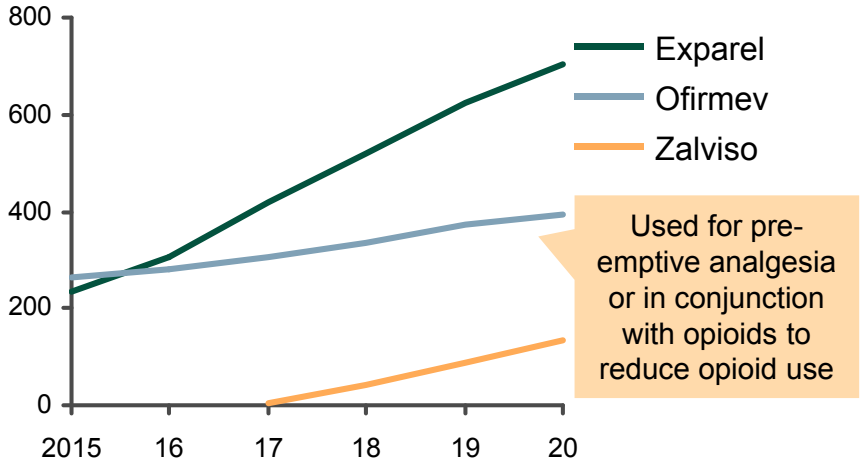
Post-operative pain

DRAFT

Reduction of opioid use and better POP treatment practices are the underlying unmet needs in POP management

Currently marketed treatments

Projected sales for key products (2015-20)
Millions of dollars



- In 2013, 60% of value sales in the POP market in Europe were generics and 50% were injectable formulations; for volume sales, 80% were generics and 90% were oral
- Paracetamol dominated both the value and volume sales
- The POP market is expected to grow with growing use of novel non-opioid products, such as Exparel
- A key trend for the POP market will be the replacement of opioids with multimodal analgesia and long-acting local anaesthesia, driven by attempts to shift towards early patient discharge and more outpatient procedures

Key unmet needs

- **Reliance on opioids** has been a key unmet need for POP management, as it is associated with prolonged hospital stay, tolerability and dependency issues
  - this unmet need will be better addressed with the growing use of multimodal analgesia, aiming to reduce opioid dosage through a combination of synergistic medications
- POP is **generally under-treated,** with surveys reporting moderate-to-severe pain in 80-90% of inpatients; this is likely related to several unmet needs in the current SoC
  - **no local anaesthetics** are able to **maintain high efficacy** for the first 48-72 hours following surgery
  - **IV PCA** has been associated with **safety issues**, such as pump failure, malfunction, human error, increased risk of infection, as well as **reduced patient mobility**
  - there are **variations in prescription patterns** in the post-operative setting and lack of use of multimodal analgesia in some institutions due to lack of a specific policy
- Overall, the unmet need of **lowering opioid use** is **likely to be reduced** in the future with the use of multimodal analgesia, although there is likely to be **room for a new non-opioid, non-IV, long-acting product**

Source: Botti *et* al. (2014) Implementation Science; Cowen; EvaluatePharma

Post-operative pain

DRAFT

The POP pipeline is relatively large; while most assets are not expected to impact SoC, some, including long-acting local anaesthetics, could provide convenient efficacy

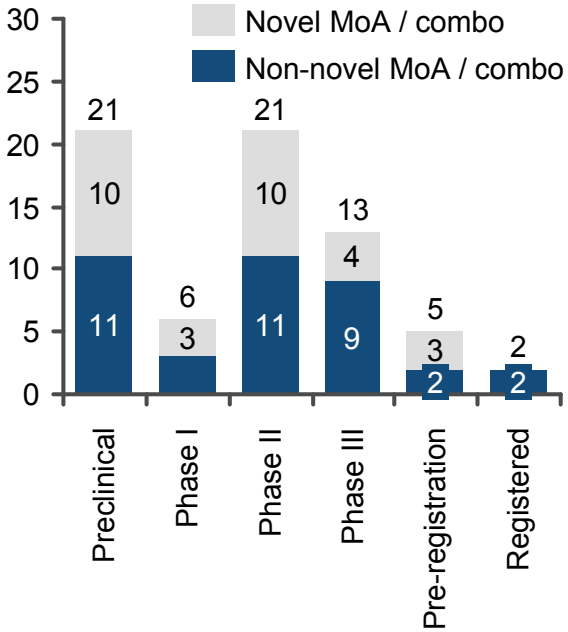
Typical clinical trial design, timing, size

- POP drugs are typically tested across a number of Phase II / III trials settings
  - typical settings include various abdominal surgeries, breast surgery, knee surgery, et~
  - the setting is important as it may have an effect on the outcome, e.g. surgeries that cause less pain may be less likely to show significance
- Typical primary endpoints include pain intensity on NRS*, mean pain intensity over a period as recorded on an electronic diary, total morphine-equivalent dose for supplemental analgesia over a period, and SPID* over a period, among others
- Importantly, failure of a proportion of the studies will not necessarily preclude approval but may lead to a narrower indication**

Phase	Avg enrolment	Avg length (mo)
I	96	21
I / II	60	28
II	88	20
II / III	112	27
III	206	22

Current pipeline

POP pipeline (February 2016)
Number of assets



- The most notable assets in the POP pipeline are local anaesthetics
- Posidur is a CR bio-erodible polymer of bupivacaine by Durect
  - Durect initiated another Phase III trial in 2015, following prior failure and FDA's request
- HTX-011 is ER bupivacaine + meloxicam (a COX-2 inhibitor) by Heron Therapeutics
  - meloxicam's role is to prevent deactivation of bupivacaine by local inflammation and extend efficacy beyond 24 hours
  - Heron initiated a Phase II trial in 2015; preliminary results have shown that HTX-011 significantly reduces pain and opioid need
- Other assets in the pipeline include an EGR1 transcription factor inhibitor, sublingual buprenorphine and the biased ligand opioid oliceridine
  - AYX-1 (Adynxx) inhibits persistent movement-evoked POP, aiming to reduce chronic pain risk with a single injection during surgery (Phase II)
  - Insys's sublingual buprenorphine (Phase III) and Trevena's IV oliceridine (TRV-130, Phase III) are two late-stage opioids in development for POP

Note: *NRS: numerical rating scale; SPID; summed pain intensity scores. ** For example, failure of several Phase II studies resulted in Exparel's approval only for bunionectomy and hemorrhoidectomy.
Source: Cowen; clinicaltrials.gov, Pharmaprojects

What is the ideal TPP for a POP asset?

A TPP for the ideal POP asset	
Value proposition	• Local administration once during surgery with an analgesic effect for at least 72 hrs post-surgery • No systemic effects, such as those related to opioid use, that could prevent timely discharge • No patient mobility issues, such as those related to IV tethering
Indication and usage	• Indicated for post-operative pain management • Capable of being applied to a wide range of surgical procedures
Administration and dosing	• Administered locally through injection or administered once during surgery
Efficacy	• Efficacy non-inferior to currently-used opioid SoC with a 72 hour duration post-surgery • Efficacy post-72 hrs not desirable as it can delay physical therapy or may lead to concomitant sensory block
Safety and tolerability	• No significant harmful effects, such as those related to opioid use (nausea, constipation) • No safety issues, such as those associated with IV PCA (pump failure, malfunction, human error, and increased risk of infection)
Pricing and reimbursement	• Good pricing potential for a novel long-acting local anaesthetic as only one has currently been approved in the US and has questionable efficacy post-24 hours following surgery

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain`
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia`
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

Procedural pain

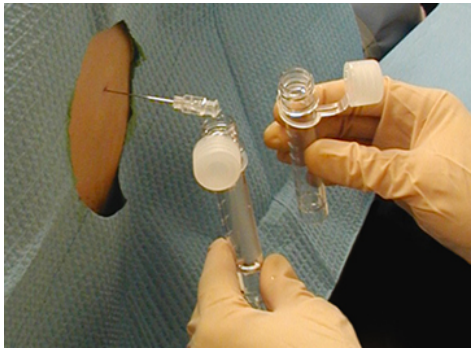
DRAFT

There is little unmet need to address in procedural pain, other than inconsistent application of comfort measures by HCPs, making it a market with limited attractiveness

Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• Unmet need mostly driven by sub-optimal management of procedural pain by HCPs. Little unmet need for pharmacologic treatments, mostly relevant for procedures that require opioids
Validation of disease & treatment		20%	• Procedural pain is most likely to have nociceptive origin. However, it can also be related to anxiety before and during the procedure, which is why procedural pain management is also referred to as “comfort management”
Competitive intensity		10%	• Market penetrated by many generics. Pipeline overlaps with anaesthesia and POP but no assets that will significantly impact the SoC were identified
Market opportunity		10%	• Just under 10m selected procedures likely took place in the US and EU5 in 2015, although the total addressable population is much larger if needle stick and other procedures are added. Pricing likely to be affected by generics
Probability of clinical trial success		10%	• Clinical trials appear to have well-established primary endpoints. Such endpoints have also been developed for paediatric trials, which constitute 30% of the investigated trials for procedural pain
Overall attractiveness			• ***Relatively low overall unmet need.*** The unmet need does not revolve around better pharmacologic treatment but rather around the inconsistent application of procedural pain comfort measures by HCPs

Procedural pain is associated with procedures that require various degrees of anaesthesia and analgesia, such as needle stick procedures or fracture reductions

Indication overview

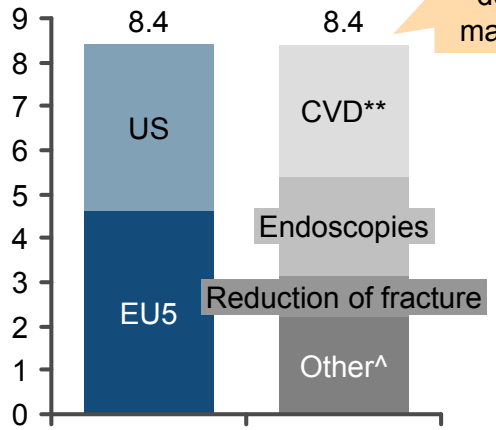


- Any procedure with actual or potential tissue damage may cause procedural pain
- Procedural pain can range from mild to severe and may be influenced by the patient's age, gender, culture, emotional and psychological state, anxiety level, understanding of the procedure, et~
- Procedures that may cause pain include simple procedures, such as venipunctures, immunisations, and more invasive ones, such as lumbar punctures, fracture reductions, biopsies
- These procedures may be performed in the hospital or ambulatory clinic, physician office or at home
- Management of procedural pain is important, as its improper treatment may lead to harmful immediate and long-term effects
- Long-term effects include experiencing more pain during subsequent procedures (hyperalgesia), insomnia, depression, changes in appetite, et~

Epidemiology

Estimate of a subset of procedures in the US and EU5 (2015)

Millions of procedures*



Analgesia will be relevant to a subset of procedures, depending on the need to manage the associated pain

INDICATIVE

The growth of this subset of procedures is likely to be nearly flat in the near future

- It is estimated that 8.4m minimally invasive cardiovascular procedures, endoscopies, obstetric laceration repairs and fracture reductions took place in the US and EU5 in 2015
- There are a number of additional procedures (punctures, immunisations, biopsies) that could increase the overall size of the addressable population for analgesia, if pain is addressed
- Depending on the procedure, anaesthesia alone or anaesthesia combined with analgesia may be required
- For example, short painful procedures, such as wound dressing, may require minimal anaesthesia but be complemented with some analgesia to manage the associated pain

Note: *Estimated using US procedures per 10K of population extrapolated to EU5 population size. **Includes coronary angioplasty or atherectomy, coronary artery stent insertion, cardiac catheterization, pacemaker insertion. ^Includes repair of obstetric laceration.

Source: CDC; Medscape

Procedural pain can be managed pharmacologically or with alternative interventions; children and the elderly are especially vulnerable to experiencing such pain

Disease aetiology / pathophysiology

- Procedural pain is most likely to be nociceptive and result from tissue damage during the procedure
- However, it may also be related to anxiety and psychological distress

Special attention has to be paid to the management of procedural pain in neonates, infants, young children and elderly who are especially vulnerable to it due to communication limitations, and in whom improperly managed procedural pain may lead to long-term harmful effects. Non-pharmacologic methods, as well glucose/sucrose, are most often used in paediatric patients to avoid use of pharmacologic methods.

Current treatment paradigm

Pharmacologic options

Local anaesthetics

- Injected subcutaneously or intradermally or applied topically on the skin (e.g. for needle stick procedures, such as intravenous catheter insertion, suturing, biopsies)
- For invasive procedures, administered through regional anaesthetic techniques
- Examples include bacteriostatic saline, lidocaine, lignocaine, tetracaine, prilocaine

Non-opioid analgesics

- NSAIDs (e.g., ketorolac or ibuprofen) for moderate pain and acetaminophen alone for mild pain
- Both may be used in combination with opioids, anxiolytics, sedatives

Opioid analgesics

- For moderate-to-severe procedural pain and usually administered intravenously
- The most commonly used opioids are fentanyl, hydromorphone, and morphine

Procedural sedation

- For moderate-to-severe procedural pain with or without extended periods of immobilization
- Typically anxiolytics and sedatives (e.g. benzodiazepine) are used but they not provide analgesia

- The ASPMN has recommended that procedural pain is managed through a combination of pharmacologic and non-pharmacologic methods, where the latter supplement the former
- The management plan should be prepared based on the patient's unique characteristics, care setting, procedure being performed, and skill of the HCP performing the procedure
- For less invasive procedures, local anaesthetics, NSAIDs, acetaminophen, opioids, anxiolytics and sedatives are the pharmacologic options of choice as opposed to regional and general anaesthesia for more invasive and painful procedures
- Non-pharmacologic options include relaxation, meditation, imagery, massage, and music, but more research is needed to establish the usefulness of non-pharmacologic interventions in various procedural pain settings

Non-analgesic effect

Source: American Society for Pain Management Nursing; Medscape

Procedural pain

DRAFT

The unmet need in procedural pain is mostly related to sub-optimal HCP pain management, rather than a need for additional pharmacologic options

Currently marketed treatments

- In the anaesthesia market, generic products have been gaining market share from branded products
  - lidocaine and chloroethane are leading generics
- This generic competition has led to slight market decline in the EU5 between 2010-13
- However, EMLA, a branded dermal anaesthetic comprised of lidocaine/prilocaine, is still one of the largest products
- The anaesthesia market is not expected to significantly grow in the future as no new products are expected to change the SoC

Key unmet needs

- The unmet need for procedural pain is **principally centred around better management of procedural pain by HCPs**, rather than better pharmacologic interventions
  - studies have shown that **healthcare providers often do not have guidelines** for procedural pain management or do not follow them consistently
  - recent reports of pain management in children subjected to painful procedures suggest that **pain is inconsistently assessed and inadequately managed in a majority of paediatric patients**
  - in addition, **underuse of topical anaesthetics and insufficient time to administer** a medication have been shown to occur
- In terms of pharmacologic interventions, the unmet need is **likely to be highest for procedures that require opioid analgesics**, whose use is associated with adverse side effects

Source: American Society for Pain Management Nursing; American Academy of Pediatrics; Management; Medscape

Many clinical trials for procedural pain focus on paediatric patients and non-pharmacologic interventions; the pipeline is not expected to change the SoC

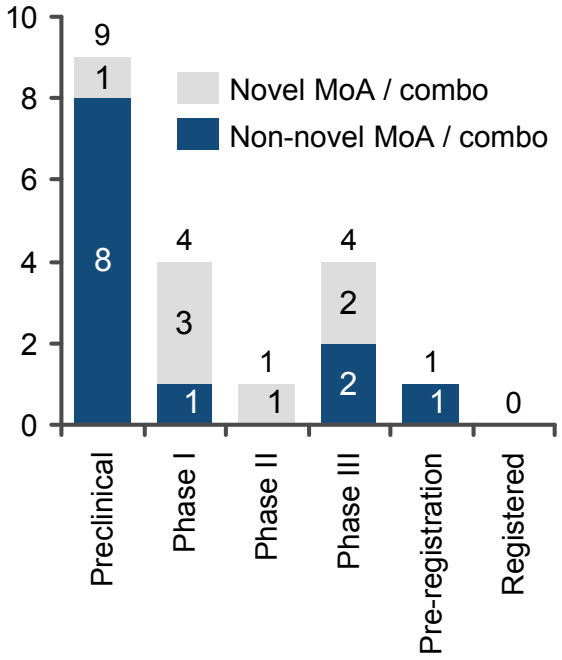
Typical clinical trial design, timing, size

- Trial settings include immunisations, veni-punctures, biopsies, catheterisations, and colonoscopies
- About 30% of of the clinical trials investigated for procedural pain involve paediatric patients, and about 30% of these paediatric trials test non-pharmacologic interventions
- Primary endpoints used for paediatric trials include pain intensity assessed through VAS* scale, NCCPC-PV* scale, and Premature Infant Pain Profile (facial expression, heart rate, oxygen saturation, blood pressure)
- Primary endpoints in other trials include pain intensity assessed through VAS and NRS, time to request for rescue analgesia, RASS*, SAPS scale, et~
- These endpoints appear relatively well-defined

Phase	Avg enrolment	Avg length (mo)
I	58	36
II	96	37
II / III	179	39
III	603	21

Current pipeline

Anaesthesia pipeline (February 2016)
Number of assets



For POP pipeline, please see the relevant section

- Both the POP and anaesthesia pipelines contain local anaesthetic, opioids, non-opioids and sedatives that may be relevant for procedural pain
- APIs include bupivacaine, tetracaine, benzodiazepine, remimazolam
- Few assets appear to be specifically intended for procedural pain
- AcelRX was developing ARX-03 for procedural pain but appears to have refocused on two other products, ARX-04 and Zalviso
- Kovacaine Mist, a fixed-dose nasal spray of tetracaine and oxymetazoline, is under development by St Renatus for dental anaesthesia (Phase III)
- Overall, there appear to be no products in the pipeline that will significantly impact the SoC

Note: * NCCPC-PV scale: non-communicating Children's Pain Checklist; VAS: Visual Analogue Scale; RASS: Richmond Agitation Sedation Score; SAPS: Self-Administered Patient Satisfaction.
Source: Cowen; clinicaltrials.gov, Pharmaprojects

What is the ideal TPP for a procedural pain asset?

A TPP for the ideal procedural pain asset	
Value proposition	• Convenient administration once before the procedure with a potent anaesthetic effect • Ability to reduce opioid analgesic use before or after the procedure
Indication and usage	• Indicated for procedural pain and potentially for POP management • Capable of being applied to a wide range of procedures
Administration and dosing	• Easy administration, e.g. a topical cream, a transdermal patch, a spray • Administered once before the procedure
Efficacy	• Efficacy as good as currently used SoC in anaesthesia
Safety and tolerability	• No significant harmful effects, such as ones related to opioid use (nausea, constipation) • Safe to administer on children and elderly patients
Pricing and reimbursement	• Price likely to be squeezed by generics but there may be some higher pricing potential for an asset with high efficacy and convenient route of administration

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1	2	3	4	5
Neuropathic pain	Non-autoimmune musculoskeletal pain	Autoimmune joint disease	Cancer pain	Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6	7	8	9	10
Procedural pain	Trauma pain	Migraine	Fibromyalgia	Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

Trauma pain

DRAFT

Limited unmet needs and a highly genericised market make trauma pain a lower priority opportunity for additional expansion beyond Penthrox

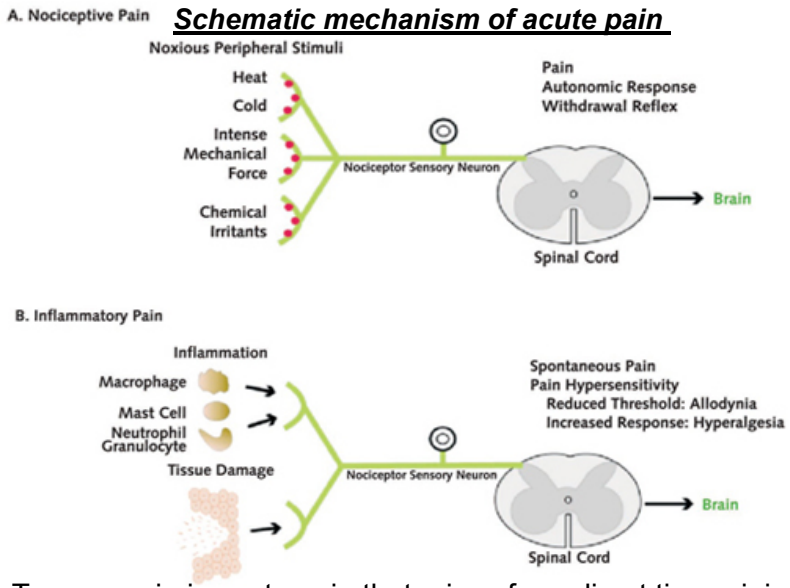
Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• Treatment paradigms are very well established, with physicians comfortable with managing pain in injury/trauma. Some unmet needs in route of administration but need is limited, especially given recent Penthrox launch
Validation of disease & treatment		20%	• Well-established knowledge of the cause of pain in trauma and injury; well-established knowledge of the physiological processes of acute nociceptive pain
Competitive intensity		10%	• Highly genericised treatment algorithm with well established NSAID and opioid treatment options make this a mature and competitive market. Limited pipeline assets
Market opportunity		10%	• Large patient population of 100m due to high incidence of road traffic accidents and traumatic injury. Limited patient population growth. However, high generic penetration limits pricing potential
Probability of clinical trial success		10%	• Regulatory hurdle is easier than other pain indications due to lower enrolment numbers, shorter treatment duration, well established end points. Most products approved for a broad acute pain indication
Overall attractiveness			• Despite high prevalence, trauma pain is an opportunity with limited attractiveness due to ***well established and highly genericized treatment paradigms***. Some opportunities may exist for reformulations; however, low pricing potential may limit revenues

Trauma pain

DRAFT

Due to high incidences of traumatic events, trauma pain is a prevalent condition across global markets

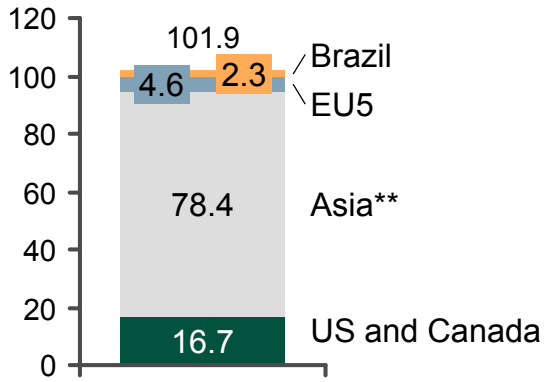
Indication overview, aetiology and pathophysiology



- Trauma pain is acute pain that arises from direct tissue injury resulting from physical trauma. Traumas include, but are not limited to road traffic accidents and burns and open wounds
- Trauma pain ranges from mild (simple injuries) to severe (broken bones)
- Tissue injury triggers acute nociceptive pain pathways, typically lasting 2-4 weeks depending on severity
- Moderate to severe trauma pain is treated by a range of specialists, e.g. surgeons, ER and orthopaedic physicians
- This analysis focuses on moderate to severe trauma pain in the hospital setting

Epidemiology

Prevalence of trauma
Millions of patients*



INDICATIVE

Australia patient numbers based on clinical literature <50,000

- Annual hospitalisations and hospital discharges due to trauma were used as proxies to asses trauma pain incidence across geographies
- Trauma is most common in patients aged 0-44 and amongst males
- The volume of trauma patients is expected to remain relatively flat in the near term, growing at roughly the same as population growth rates

Note: * Estimated based on population above 15 yo. ** Includes Malaysia, China, Singapore, Philippines, South Korea. ^ ACR: American College of Rheumatology.
Source: WHO; CDC

DRAFT

The current treatment paradigm for moderate to severe trauma pain is well-established, with few unmet needs, mostly for quick- and long-acting, non-IV drugs

Current treatment paradigm and unmet needs

Pre-hospital moderate

- Paracetamol and codeine combination
- NSAIDs as needed
- Penthrox (AUS/EU)

In hospital

- Weak opioid/NSAID combinations +/- paracetamol
- Supplemental IV morphine if needed

Discharge

- Continue on paracetamol/codeine as needed

Pre-hospital severe

- 1st line IV opioids/morphine
- Intranasal if no IV line
- Penthrox (AUS/EU)
- 2nd line ketamine

In hospital

- Opioids/ IV morphine
- Strong opioid/NSAID combinations
- Supplemented with NSAIDs, as needed

Discharge

- 23% of patients prescribed opioids on discharge for an average of 13 days in EU/US
- Average length of hospital stay is 10 days

- Treating moderate pain in the acute trauma setting is well established with very clear guidelines
- Rate of onset, particularly for NSAIDs, and duration of pain relief are potential areas of opportunity, although physicians are satisfied with their current ability to reliably control pain in an emergency/trauma setting
- **IV route of administration** of strong **opioids is inconvenient**, particularly in a pre-hospital setting. Intranasal or inhaled products are more desirable due to convenience of RoA without sacrificing too much speed of onset
- Physicians consider self-administered pain relief to be psychologically more appealing to patients in an emergency setting
- **Accurately understanding pain severity** can be an issue for physicians, particularly in patients with severe pain and head trauma
- **Opioid addiction and abuse is not a major concern** due to short term nature of treatment

Source: NICE; British Journal of pain

DRAFT

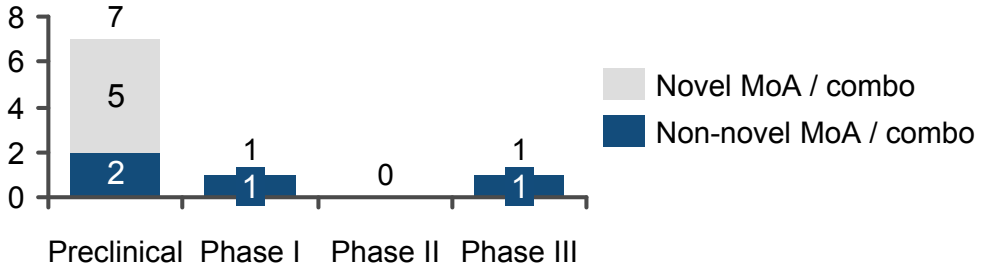
Despite relative ease of obtaining approvals, few branded products are used and the pipeline is limited

Currently marketed treatments

- The market is highly genericised, dominated by generic NSAIDs, paracetamol and opioids
- Some use of branded opioids/opioid combos in the USA, e.g. Nucynta ER and Opana ER

Current pipeline

Injury/Trauma Pipeline (Feb 2016)
Assets across trial phases



- Very few products are specifically pursuing an indication in trauma
- Current products in clinical development are inhaled formulations of opioids
- No recent approvals for products specifically for trauma; compounds are typically indicated in acute pain and used for trauma patients

Clinical trial design, timing, size

- By nature of the condition, trials in acute trauma pain are short, with most studies looking at interventions over 24-96 hours
- Study enrolment is smaller, as most studies are demonstrating efficacy and safety in reformulations/change in ROA for already licenced compounds
- Typical endpoints are similar to other pain indications, e.g. rating on the VAS, numerical rating scales
- Products used to treat trauma pain typically pursue a broader acute pain indication, rather than a specific trauma pain indication

Phase	Avg enrolment	Avg length (mo)
I	42	24
I / II	29	27
II	93	34
II / III	45	15
III	288	27

Note: * NNT: Number needed to treat.
Source: clinicaltrial.gov; Pharma projects

What is the ideal TPP for a trauma pain asset?

A TPP for the ideal NAMSP asset	
Value proposition	• Able to deliver fast-acting, long-lasting pain relief through a route of administration convenient to the patient
Indication and usage	• Indicated for moderate severe pain in injury/trauma in both pre-hospital and hospital settings
Administration and dosing	• Administrated as needed either through inhaled, intranasal or oral formulations
Efficacy	• Immediate reduction of pain equivalent to current available SOC
Safety and tolerability	• Side effect profile no worse than current SOC • Lower GI side effects than NSAIDs and opioids desirable
Pricing and reimbursement	• Priced higher than generics, but opportunities for premium pricing are limited

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1	2	3	4	5
Neuropathic pain	Non-autoimmune musculoskeletal pain	Autoimmune joint disease	Cancer pain	Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6	7	8	9	10
Procedural pain	Trauma pain	Migraine	Fibromyalgia	Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

DRAFT

The migraine market is attractive for chronic migraine prophylactics that offer better efficacy than current preventative therapies

Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• Acute medications for migraine, such as triptans, are efficacious; however, preventive therapies for chronic migraine do not meet patients' needs
Validation of disease & treatment		20%	• Aetiology and pathophysiology theories are established and have led to the development of some medications; however, full understanding of disease pathology is still lacking
Competitive intensity		10%	• Migraine-specific and non-specific agents are available for episodic migraine. For chronic migraine, however, there is only one FDA-approved treatment for prevention
Market opportunity		10%	• The total prevalent population in Mundi/Purdue territories is 230m, but many are managed on generic medications. The chronic migraine population is 15m and could support a higher price for a differentiated therapy.
Probability of clinical trial success		10%	• Clinical trial end-points are well-established both for the prevention of further attacks and the abortion of new attacks. These end-points are consistent amongst already-approved agents
Overall attractiveness			• ***High unmet need is identified in chronic migraine sufferers***, and moderate unmet need is seen in episodic migraine, leading to high market opportunity and varied competitive intensity

DRAFT

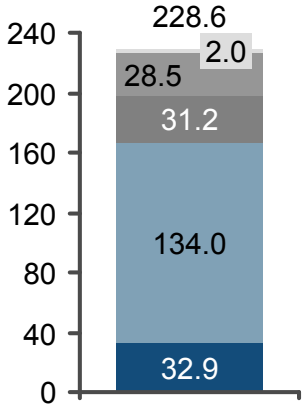
Migraine is a common condition that predominantly affects women, with a total prevalence of 230M people in geographies that Mundi/Purdue operate in

Indication overview

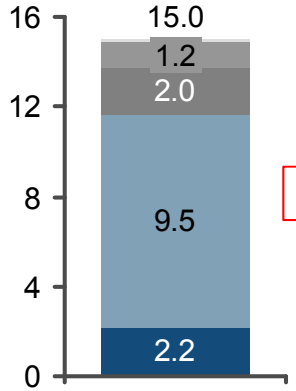
- Migraine is a neurological syndrome which causes one-sided, pulsating headaches lasting between 4 and 72 hours, which may be preceded by an 'aura' in 30% of the cases
- There are two types of migraine:
  - episodic migraine is defined as less than 15 headache days per month and is the most common type
  - chronic migraine is defined as more than 15 headache days per month, with at least 8 of them being migraine-like headaches
- Migraine is often associated with a variety of other symptoms, such as auras, nausea, vomiting, photophobia and phonophobia
- Approximately 80% of migraine sufferers are women, of whom 50% have migraines associated with menses

Epidemiology

Prevalence of total migraine (2015)
Millions of patients*



Prevalence of chronic migraine (2015)
Millions of patients*



INDICATIVE

- Across Mundi/Purdue territories, the prevalence of migraine is 230m, with 15m suffering from chronic migraine
- The diagnosis rate for episodic migraine is 60%, mostly because patients self-medicate and do not consult GPs as often, with the diagnosed population at 140m
- The diagnosis rate of chronic migraine is 20%, with potential to increase if targeted treatments become available; it is estimated that there are 3m diagnosed patients
  - nearly 90% of chronic migraine patients have consulted a doctor; 25% of those saw a headache or pain specialist
  - however, the low diagnosis rate is due to mislabelling as other chronic headache conditions (e.g. cluster headaches, medication overuse headaches) and the lack of chronic migraine specific treatments

Note: *Estimated based on population above 15 yo. ** Includes Malaysia, China, Singapore, Philippines, South Korea.

Disease aetiology and pathophysiology are partly understood. Combinations of non-specific and specific treatments are used for abortion of acute attacks and prevention

Disease aetiology / pathophysiology

- The precise aetiology and pathogenesis of migraine are partly understood
- Prominent features of the pathology are a series of neural and vascular events which lead to the activation of trigeminal pain fibres, located in the face, potentially associated with a process known as cortical spreading depression
- Neurotransmitters (e.g. dopamine and serotonin) have also been implicated in the pathology and they offer explanation to some of the symptoms associated with migraines, such as nausea and vomiting. This theory led to the development of triptans
- Full understanding of disease pathology is still lacking and the only FDA approved treatment for chronic migraine, onabotulinumtoxinA, was discovered by accident
- Partial understanding of the pathology has guided the development of treatments; however, better understanding would facilitate the development of more efficacious preventative therapies

Current treatment paradigm

Migraine SoC

1st line treatment

Pharmacologic	Other
• **Abortive treatment**: Migraine specific therapies such as triptans and ergotamines in combinations with other analgesics (e.g. NSAIDs) • **Preventative treatment of episodic and chronic migraine:** Antiepileptics (e.g. topiramate) or β-blockers (e.g. propranolol)	• Alter lifestyle to avoid triggers of migraine if possible (e.g. improve sleeping pattern) • Maintain a headache diary that assists in identifying triggers and guides diagnosis and treatment

2nd line treatment

Pharmacologic

- **Episodic migraine:** trial anti-depressants and other anti-epileptics or β-blockers
- **Chronic migraine:** Intramuscular onabotulinumtoxinA

- Most patients (80%) receiving abortive treatment are relatively well managed within 1-3 lines of triptan treatment
- 2nd line therapies are limited and, beyond onabotulinumtoxinA for chronic migraine, are guided by patient comorbidities and a practice of trial and error

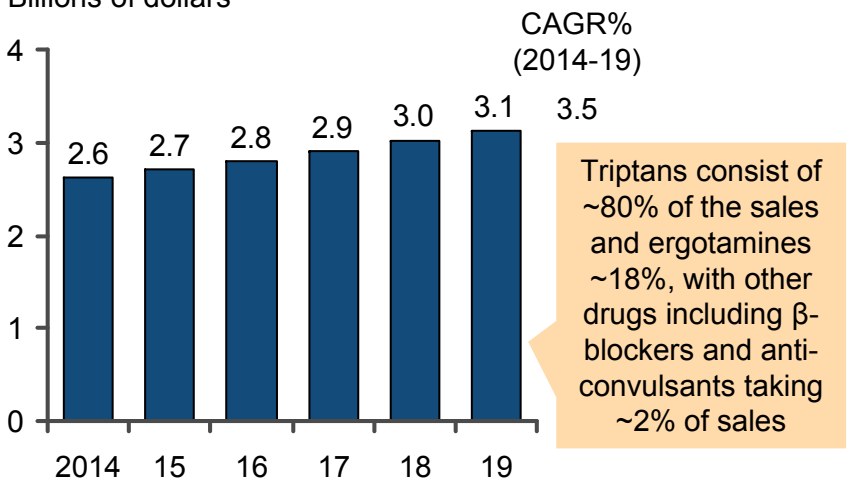
Source: American Headache Society (AHS); American Academy of Neurology (AAN); BMC Neurology

DRAFT

Increasing the efficacy of migraine prevention agents is a significant unmet need. The global market size is forecast to see moderate growth primarily driven by new products

Currently marketed treatments

Global market for migraine drugs (2014-19)
Billions of dollars



Triptans consist of ~80% of the sales and ergotamines ~18%, with other drugs including β-blockers and anti-convulsants taking ~2% of sales

- The global market is expected to see modest growth over the coming years, mostly driven by
  - novel product launches and reformulations that offer better efficacy, especially in preventing migraines
  - an increase in the global middle-aged population, who demonstrate higher prevalence of migraines
- The Americas account for ~78% of the total migraine drugs market, due to higher cost of drugs and an increase of the population of migraine sufferers
- EMEA and APAC account for ~14% and 8%, respectively

Key unmet needs

- Sufferers of **chronic migraine are inadequately managed**
  - there is a **single approved preventative therapy for chronic migraine**, onabotulinumtoxinA
  - access to this therapy is limited and restricted to patients who have failed to respond to preventative therapies used for episodic migraine
  - this therapy can reduce the number of days with headache per month from ~20 to ~12, but **fails to completely prevent migraines and is effective only in 50% of patients**
- Most episodic migraine patients receiving **abortive treatment are well-managed**; however, preventative therapies are not successful in making patients migraine-free
  - triptans have a NNT^ ~2-3; however, **consistency of response** for single patients and across patients is lacking, leading to a "trial and error" type of treatment
  - concerns over **medication overuse headaches** limit the usage of triptans and can lead to rebound headaches
  - preventative therapies such as topiramate are successful in halving the number of migraine attacks, but only ~6% of patients become migraine free
- Patients with **contraindications to triptans and ergotamines**, such as cardiovascular disease (~10% of migraine sufferers), have limited treatments available to them

Note: ^NNT: number needed to treat, i.e. number of patients who would have to take the drug for one patient to have pain relief of 50% or more. NNH: number needed to harm, i.e. number of patients who would have to take the drug for one patient to report a harmful side effect.
Source: American Headache Society; Journal of Headache and Pain; TechNavio; FDA

DRAFT

The migraine pipeline is characterised by novel MoAs, with a significant number of agents inhibiting CGRPs. Clinical trial design is consistent and well characterised

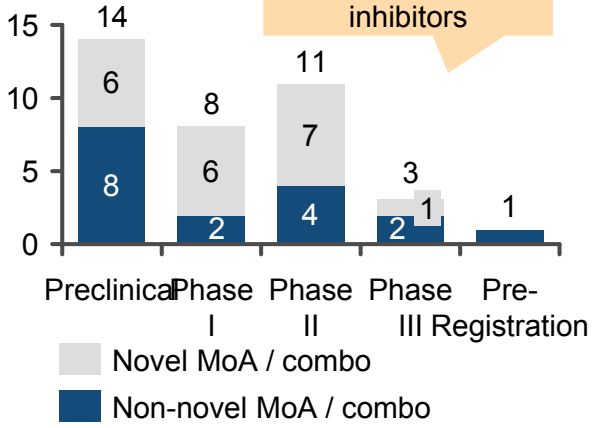
Typical clinical trial design, timing, size

- Primary efficacy endpoints are well established and appear to be consistent across studies
- In the U.S., product efficacy is usually studied against placebo, with subjective measurements of patient pain, occasionally in the form of pain diaries
- Common endpoints are:
  - change from baseline of migraine headache days per period (usually 4 weeks long)
  - degree of pain relief at regular time intervals following administration
  - change from baseline in associated symptoms i.e. nausea, vomiting, photophobia and phonophobia

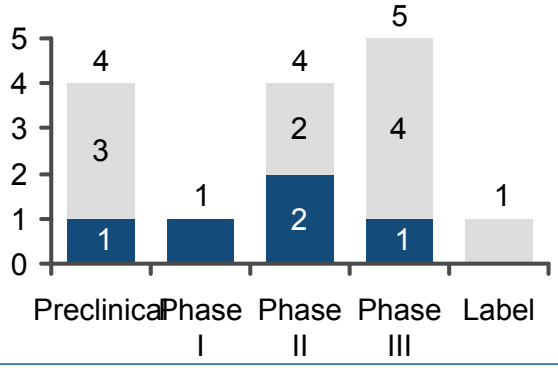
Phase	Avg enrolment	Avg length (mo)
I	110	14
I / II	28	21
II	219	23
II / III	651	44
III	561	21

Current pipeline

Abortive therapy pipeline (March 2016)
Number of assets



Migraine prevention pipeline (March 2016)
Number of assets



- Novel MoAs are prominent, with a significant proportion (33%) being CGRP^ inhibitors. This is a promising MoA stemming from better understanding of pain pathology, which could impact the SoC
- Only four of these agents have launched for any other disease globally
- Phase III assets include
  - TEV-48125 a recombinant humanized MAb targeting CGRP, under development by Teva for the prevention of chronic migraine and high-frequency episodic migraine
  - Lasmiditan, a neurally acting anti-migraine agent which targets 5HT1F receptors, under development by Colucid Pharmaceuticals

Five of the novel MoAs are CGRP inhibitors; two drugs are specifically targeting chronic migraine

Note: ^CGRP: Calcitonin gene related peptide.
Source: clinicaltrials.gov; Pharmaprojects

What is the ideal TPP for a migraine asset?

A TPP for the ideal acute migraine therapy	
Value proposition	• A targeted therapy for acute migraine attacks with higher tolerability and equal or higher efficacy than currently available treatments
Indication and usage	• Indicated for use in episodic and chronic migraine to abort or treat migraine headaches • Targeted to patients who have received a diagnosis of migraine as first-line therapy for acute attacks
Administration and dosing	• PRN oral/intranasal administration
Efficacy	• NNT* equal or lower than triptans (2-3) • Consistent response across patients
Safety and tolerability	• Higher tolerability than triptans, with no contraindication in patients with cardiovascular disease • Safe for frequent administration without medication overuse headaches and/or rebound headaches • No drug-drug interaction, allowing combination with NSAIDs or other analgesics
Pricing and reimbursement	• Although generic triptans are already available, there is potential to price higher than branded triptans for patients with cardiovascular disease

A TPP for the ideal chronic migraine therapy	
Value proposition	• A targeted therapy for the prevention of chronic migraine with higher efficacy and easier administration than currently available treatments, such as IM onabotulinumtoxinA
Indication and usage	• Indicated for use in chronic migraine in order to prevent occurrence of headaches • Targeted to patients who have received a diagnosis of chronic migraine as 2nd line for those who failed treatment with traditional prophylactic medications, such as topiramate
Administration and dosing	• Daily oral medication
Efficacy	• Reduction of headache days by at least 8 days per month, with complete resolution of migraine attacks being ideal • Effective in more than 50% of patients • Reduction of disability level, allowing return to routine daily activities and work
Safety and tolerability	• Equal or higher tolerability than currently available prophylactic agents, such as topiramate
Pricing and reimbursement	• Pricing for 2nd line therapy for chronic migraine could be significantly higher than topiramate if it is efficacious and reduces level of disability

Note: *NNT: number needed to treat.

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

DRAFT

Fibromyalgia could represent an attractive opportunity given the high unmet need; however, better understanding and awareness are required

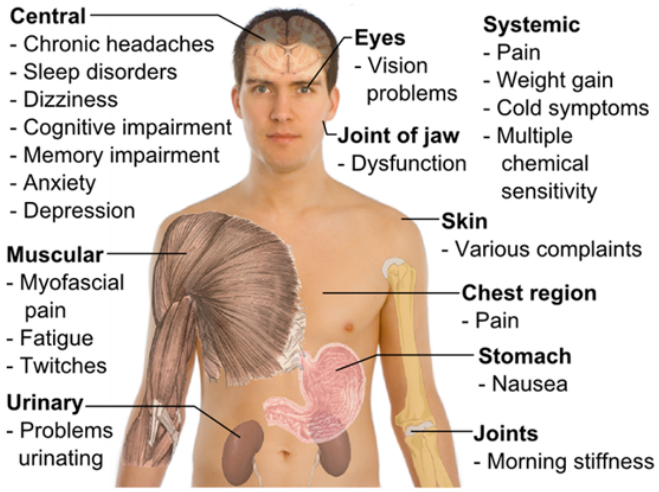
Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• No disease-modifying therapies or ones that address all symptoms, coupled with low acceptance as a diagnosis due to complexity of symptoms and diagnostic difficulties
Validation of disease & treatment		20%	• Poor understanding of aetiology and pathophysiology, which has made it difficult to develop targeted and effective treatments
Competitive intensity		10%	• Few drugs have been approved and few are effective. Limited novelty and size of pipeline. However, significant generic competition is expected as Cymbalta is generic and Lyrica will go generic in 2018
Market opportunity		10%	• ~31m people affected across MDP / Purdue geographies. Market opportunity may be more attractive in the US / Japan but uncertain in Europe
Probability of clinical trial success		10%	• Trial endpoints have not been well established and few therapies have been approved specifically for fibromyalgia. No history of approvals in Europe
Overall attractiveness			• ***Very high unmet need***. Further research on aetiology / pathophysiology for more effective therapies and improvement in QoL are required to fully benefit from this market. Awareness of the condition needs to be raised, especially in Europe, to facilitate approval of dedicated treatments

DRAFT

Fibromyalgia is a complex chronic disorder characterised by widespread pain, affecting ~31m people in the US, Canada, EU5 and parts of Asia

Indication overview

Areas affected by fibromyalgia and typical symptoms

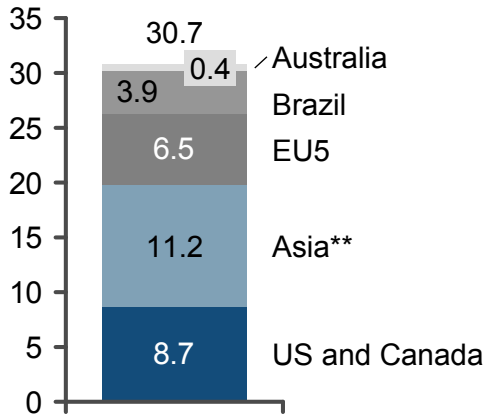


- Characterised by chronic widespread pain of muscle and connective tissue
- Often also associated with depression and anxiety
- As fibromyalgia symptoms are not restricted to pain, patients are diagnosed with Fibromyalgia Syndrome (FMS)
- Diagnosis can be controversial, as there is a lack of scientific consensus as to what causes this disease and an overlap with symptoms of other rheumatic disorders

Epidemiology

Total prevalence of fibromyalgia (2015)

Millions of patients*



INDICATIVE

We do not expect significant growth in prevalence in the near future

- The global mean prevalence is 2.7% with the mean being 3.1% in the Americas, 2.5% in Europe and 1.7% in Asia
- More than 80% of diagnosed patients are women, and the risk of fibromyalgia increases with age
- The 2010 ACR criteria base diagnosis on a WPI and a SS^, with symptoms for at least 3 months
- Compared to prior diagnostic criteria, the 2010 criteria exclude presence of "tender points", allow less pain, and include patient-reported somatic symptoms and cognitive difficulties, but this has not significantly affected the diagnosis rate

Note: * Estimated based on population above 15 yo. ** Includes Malaysia, China, Singapore, Philippines, South Korea. ^ ACR: American College of Rheumatology, WPI: Widespread Pain Index, SS: symptom severity scale.

Source: Queiroz (2013) Current Pain and Headache Reports

DRAFT

Disease aetiology and pathophysiology are poorly understood; consequently, often off-label, non-specific analgesic treatment is the approach

Disease aetiology / pathophysiology

- Poorly understood aetiology and pathogenesis
- Dysfunction of the central and autonomic nervous systems, neuro-transmitters, hormones, immune system, external stressors, and psychiatric aspects, among other factors, are all believed to be involved
- Fibromyalgia is not associated with inflammation and patients do not develop tissue damage or deformity
- Disease is characterised by aberrant pain processing resulting in chronic pain
- Pain is caused by central sensitization, blunting of inhibitory pain pathways and alterations in neurotransmitters
- Often accompanied by alterations in sleep pattern and changes in neuro-endocrine transmitters (serotonin, substance P, cortisol, et~)

Current treatment paradigm

Fibromyalgia SoC

1st line treatment

Pharmacologic	Other**
Analgesics (e.g. tramadol)	Aerobic exercise
SNRI (e.g. Cymbalta, Savella)	Cognitive behavioral therapy
Anti-epileptics (e.g. Lyrica)	
TCAs (e.g. amitriptyline)	

2nd line treatment

- ***Opiates***
- ***Muscle relaxants***

- Successful treatment can be difficult as the exact cause of the disease is unknown
- Guidelines* emphasise the importance of a multi-disciplinary management with pharmacologic and non-pharmacologic strategies
- However, generally addressing the pain takes precedence over physical or psychological symptoms

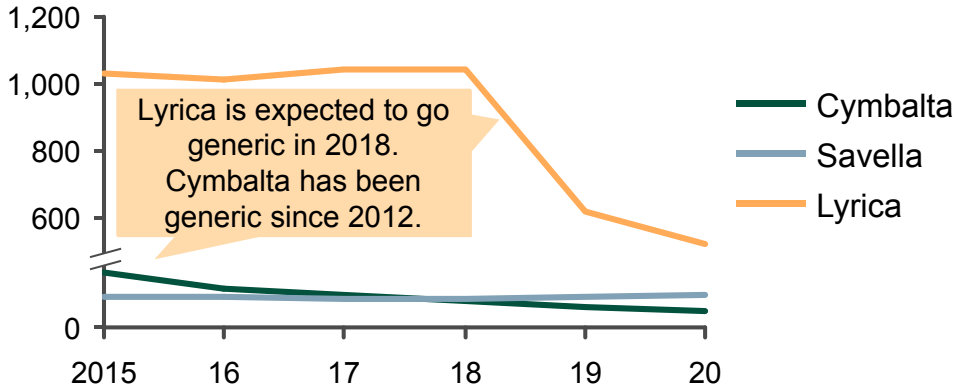
- Typically, pharmacological agents that modulate central pain processing pathways are used
- Acetaminophen and tramadol are often used off-label, although not indicated for fibromyalgia
- Opiates and muscle relaxants are used for treatment-resistant patients

Note: *American Pain Society (APS) and European League Against Rheumatism (EULAR) guidelines. ** Continues if patient progresses to second line treatment.
Source: Bellato *et* al (2012) Pain Research and Treatment; Jahan *et* al (2012) Oman Medical Journal; Medscape

There is high unmet need in fibromyalgia, given the lack of efficacious or disease-modifying therapies and physicians' limited understanding of the disease

Currently marketed treatments

Projected WW FM* sales for branded products (2015-20)
Millions of dollars



- The overall market in the US, EU5 and Japan is not expected to grow significantly; prevalence growth is expected, in line with population growth, but pricing potential will be suppressed by generics
- There are only three approved fibromyalgia treatments:
  - Cymbalta (duloxetine hydrochloride, Eli Lilly), an SNRI, was FDA-approved for fibromyalgia in 2008
  - Lyrica (pregabalin, Pfizer), a calcium channel agonist, was approved for fibromyalgia in 2007 (U.S.) and 2012 (Japan)
  - Savella (milnacipran, Forest Laboratories), an SNRI, was launched in the U.S. in 2009 for the treatment of fibromyalgia
- Many drugs are also used off-label, especially in Europe, where there have been no approvals for fibromyalgia

Key unmet needs

- **Limited understanding** of disease aetiology and patho-physiology
- **Difficult diagnosis** with no consensus among experts on screening routes - no specific diagnostic laboratory tests or biomarkers are available
- **Low physician awareness** of disease, leading to excessive testing and inappropriate treatment
- **Moderate efficacy** of available therapies, e.g. NNT for Cymbalta is ~6, for Savella 8-10, and for Lyrica ~10 but may be higher depending on the dose
- **Low tolerability** of currently available therapies, e.g. NNH for Cymbalta is 6-18, for Savella 7-14, and for Lyrica, ~6, but mostly an issue for opioids
- Lack of ability of any single current therapy to **address multiple symptoms simultaneously**, e.g. fatigue, sexual dysfunction, cognitive impairment
- Lack of **disease-modifying therapies**
- Lack of **socio-medical acceptance**, affecting QoL, as patients may have to face disbelief and distrust about the legitimacy of their illness

Note: * FM, fibromyalgia.
Source: Garcia-Campayo *et* al. (2008) Arthritis Research & Therapy; GlobalData; EvaluatePharma; FDA; FierceBiotech; EMA; Fibromyalgia.com; Medscape; National Pain Report

DRAFT

The fibromyalgia pipeline is mostly comprised of assets previously approved for other indications and is not expected to significantly impact the SoC

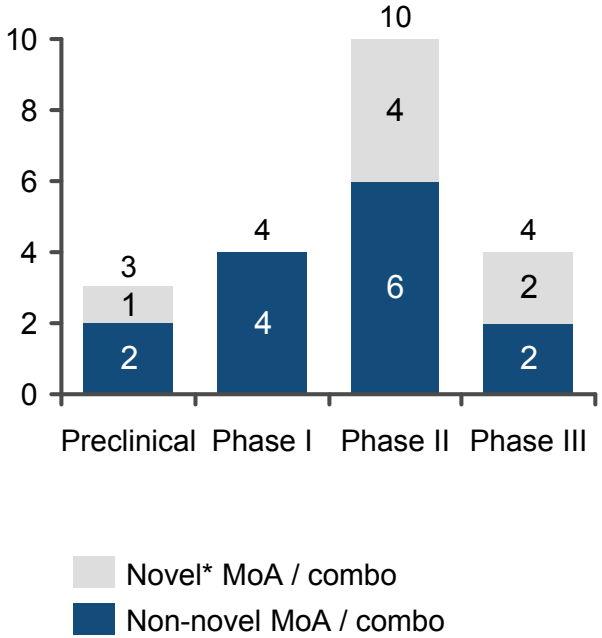
Typical clinical trial design, timing, size

- Primary efficacy endpoints in late stage fibromyalgia trials are not well defined and there is little consistency among trials
  - number of tender points
  - time to loss of therapeutic response based on pain response relative to baseline
  - average perceived pain over a certain time frame
  - abnormal values in haematology, serum chemistry, urinalysis parameters
- The US and Japan appear more willing to approve drugs for fibromyalgia
- No history of approval in Europe due to lack of recognition of fibromyalgia as a discrete condition
- Applications to the EMA were submitted and rejected for both Cymbalta and Lyrica

Phase	Avg enrolment	Avg length (mo)
I	42	20
I / II	56	25
II	140	28
II / III	202	36
III	369	27

Current pipeline

Fibromyalgia pipeline (March 2016)
Number of assets



- The majority of products in the fibromyalgia pipeline are not novel MoAs / combinations
- Many have been FDA-approved for other indications, such as depression and Parkinson's
- The only notable novel MoA is a sodium channel antagonist, BIA-2-093 by Bial, in Phase II
- Phase III assets include
  - TNX-102, a very low dose formulation of cyclo-benzaprine by TONIX Pharmaceuticals
  - irogabalin (DS-5565), an alpha 2/delta ligand by Daiichi Sankyo
  - a controlled-release (CR) formulation of pregabalin by Pfizer
- Analysts do not anticipate that products in development for fibromyalgia will significantly impact the SoC

Note: * Includes MoAs and MoA combinations that have not been previously launched for pain.
Source: clinicaltrials.gov; Fibromyalgia.com; Pharmaprojects

What is the ideal TPP for a fibromyalgia asset?

A TPP for the ideal fibromyalgia asset	
Value proposition	• A targeted and/or disease-modifying therapy with improved efficacy over currently-available treatment options
Indication and usage	• Indicated for fibromyalgia • Capability to address multiple symptoms of fibromyalgia, which is critical for a complex disease
Administration and dosing	• Oral administration to achieve systemic effect, given the involvement of multiple joints • Once daily or less frequent dosing (dosing for Cymbalta and Lyrica is once/twice daily)
Efficacy	• NNT* lower than 6 (the current NNT of the best-performing first-line therapy, Cymbalta) • Improved efficacy across fibromyalgia symptoms and, ideally, disease-modifying potential, which could avoid progression to opioid therapy in fibromyalgia patients
Safety and tolerability	• NNH* not worse than 6 (the current NNH of the best-performing first-line therapy, Cymbalta) • Side effects comparable to current first-line anti-depressant and anti-epileptic therapies, and improved over second-line opioid therapies
Pricing and reimbursement	• Pricing potential for a new therapy may be limited by genericisation of pregabalin and duloxetine

Note: * NNT: number needed to treat, i.e. number of patients who would have to take the drug for one patient to have pain relief of 50% or more. NNH: number needed to harm, i.e. number of patients who would have to take the drug for one patient to report a harmful side effect.

Ten broad categories of indications in pain were evaluated

Not exhaustive

List of broad indication segments with examples of sub-indications

1 Neuropathic pain	2 Non-autoimmune musculoskeletal pain	3 Autoimmune joint disease	4 Cancer pain	5 Post-operative pain
Diabetic neuropathy	Back pain	Ankylosing spondylitis	Breakthrough cancer pain**	Post-operative pain
Post-surgical neuropathy*	Osteoarthritis	Rheumatoid arthritis	Chemo-induced neuropathy**	Local anaesthesia
Post-herpetic neuralgia				

6 Procedural pain	7 Trauma pain	8 Migraine	9 Fibromyalgia	10 Visceral pain
Procedural pain	Emergency pain	Chronic migraine	Fibromyalgia	Chronic visceral pain
		Acute migraine		Sickle cell pain

Note: * Includes phantom limb pain. ** May include opioid-refractory cancer pain.
Source: Clinicaltrials.gov; IMS; PharmaProjects

Visceral pain

DRAFT

Pain relief in visceral pain is inadequate and diseases poorly understood. Modifying disease activity, thus indirectly alleviating pain is the top priority

Criteria	Level	Weight	Rationale
Degree of unmet need		50%	• Variable unmet need for pain relief. It is higher in common conditions with low understanding of the underlying pathology. Unmet need was higher for agents that reduce overall disease activity
Validation of disease & treatment		20%	• Visceral pain is poorly understood with low validation through available treatments. There is a considerable overlap of treatments available, including antidepressants and antiepileptics, in the poorly understood chronic diseases
Competitive intensity		10%	• Competition amongst analgesics is low, because overall efficacy is inadequate and variable, however agents that target disease activity will indirectly compete with analgesics and reduce their need
Market opportunity		10%	• Prevalence of chronic visceral conditions is high with hundreds of millions of patients affected in Mundi / Purdue territories, however variation in pathology within indications might require that drugs target smaller groups of patients
Probability of clinical trial success		10%	• Analgesia for visceral pain is mostly achieved by using common analgesics and agents which reduce overall disease activity. The lack of visceral pain specific analgesics in the pipeline suggest that the approval pathway is unclear
Overall attractiveness			• ***The unmet need to treat visceral pain is moderate*** and analgesics that relieve visceral pain, without modifying disease activity are not top priority. Also, further research is required to increase our understanding of the underlying disease in order to provide more targeted analgesia

Visceral pain is common and can present as a result of many diseases. We have identified diseases with high unmet need and market opportunity

Abdominal visceral pain

- Abdominal pain is the most prevalent type of visceral pain
- Causes of abdominal visceral pain include the irritable bowel syndrome (IBS), inflammatory bowel diseases, ischaemic bowel and cancer
- This analysis focuses on IBS because it is a chronic disease, with high prevalence (14.1% in the U.S.) and pain is one of its prominent features along with altered bowel habits
- Medications for IBS pain are targeting disease pathology directly and are also treating bowel habit symptoms

Pelvic visceral pain

- Pelvic visceral pain is caused by insults to the genitourinary system and includes conditions such as dysmenorrhea, chronic pelvic pain (CPP), endometriosis, kidney stones, bladder infections and cancer
- This analysis focuses on CPP because of the similarity between treatment of CPP and other poorly understood chronic pain indications such as chronic pain syndrome or fibromyalgia, and the high level of need to develop treatments with efficacy both in prevention and abortion of pain
- CPP is defined as pain that occurs below the belly button in women that lasts for at least six months. It is not cyclical although it may be presenting with other menstrual complaint. It's aetiology is not fully understood and it may or may not be associated with menstruation. Response to treatment is poor

Chest visceral pain

- Chest visceral pain is caused by insults to the heart, the great arteries, the oesophagus and occasionally the lungs
- This analysis focuses on stable angina as it a chronic condition that requires PRN self-medication for pain relief, unlike other presentations of visceral chest pain which tend to require emergency admission such as myocardial infarction
- Stable angina is caused by narrowing of the arteries that supply the heart, with pain arising whenever there is increased stress on the heart tissue
- Currently pain relief is provided by short-acting nitrates, taken PRN before exertion or during chest pain

Other chronic visceral pain

- Conditions that affect multiple organs can cause pain visceral pain spread across the human body, such as haematological conditions, including sickle cell disease and severe anaemia, and cancer which affects several organs
- This analysis focuses on chronic pain caused by sickle cell disease because at least one in five patients affected by this common genetic disease experience daily pain

Visceral pain

DRAFT

IBS is a common condition with associated pain that affects ~50m in Mundi/Purdue territories, with a large unmet need to develop treatments with higher efficacy

Disease aetiology / pathophysiology

- The pathophysiology of IBS is not clear
- IBS is thought to be the result of increased bowel motility and visceral hyperalgesia, enhanced by psychiatric disturbances frequently seen in IBS
- The aetiology is also poorly understood; theories range from infection, neurotransmitter imbalances and dietary intolerances

Key unmet needs

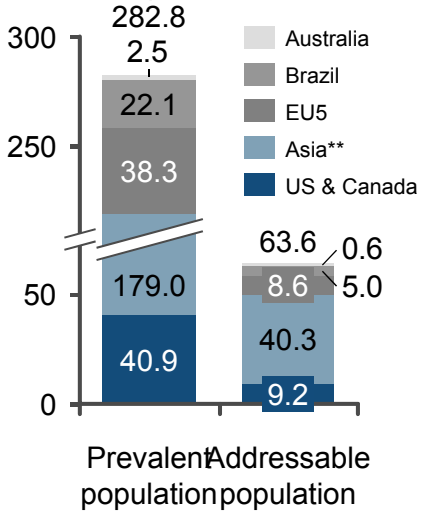
- IBS is poorly managed with a high degree of unmet need, due to the **limited efficacy** of current non-pharmacological and pharmacological therapies
- New treatments need to **address both the pain and the symptoms of constipation or diarrhea**
- Current treatments have an **inconsistent response** across various drugs requiring a period of trial and error
- Current treatments also require **frequent dosing**, with up to four times a day for some antispasmodics, hence medications with longer-lasting effects are needed

Current treatment paradigm

- The current standard of care includes non-pharmacologic and pharmacologic treatments
- There are no IBS-pain-specific drugs; pain is managed by treating the underlying condition
- Most first-line therapies for IBS are non-pharmacologic (e.g.education, dietary changes, exercise and psychotherapy)
- Pharmacological treatments address symptoms and include
  - antispasmodics, such as Gasmotin to decrease bowel motility, abdominal pain and bloating
  - antidepressants, such as tricyclic antidepressants, to reduce abdominal pain
  - anti-diarrhoeal agents and laxatives

IBS market opportunity and pipeline

Prevalence of IBS* (2015)
Millions of patients



- ~280m patients are affected by IBS Mundi/Purdue territories, although records of prevalence vary widely
- 25% are experiencing severe frequent abdominal pain and ~20% seek medical help, suggesting that the addressable population would be between 40-60m
- The pipeline consists of 33 products, which target IBS and may eliminate pain through modifying disease activity
- Pain level is a frequent endpoint in clinical trials and a measure of disease activity
- Traditional analgesics are absent from the pipeline, due to their poor efficacy in IBS and lack of addressing symptoms beyond pain

Note: *U.S. prevalence is applied to all geographies
Source: Nature Reviews Rheumatology

DRAFT

CPP is a common condition with efficacious 1st line treatments, but limited evidence to support 2nd line and disease-specific pain treatments

Disease aetiology / pathophysiology

- The pathophysiology of CPP is not clear
- Aetiology theories include vascular pelvic congestion, adhesions, musculoskeletal nerve related disorders and psychosomatic factors
- CPP may be associated with a combination of conditions, such as endometriosis or IBS
- The treatment of these occasionally cures CPP; however, the mechanism is unclear

Key unmet needs

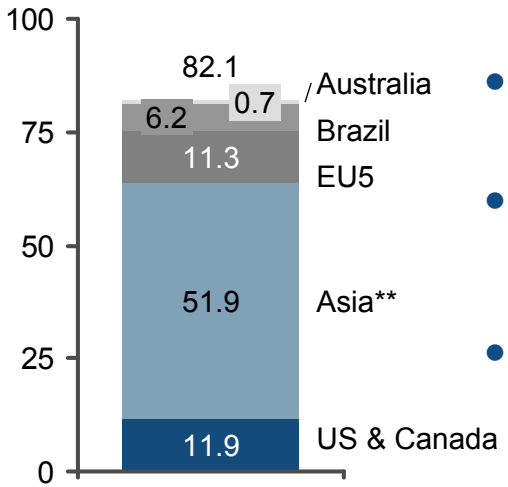
- **Developing drugs that target specific CPP pathology, tailored to each patient, and demonstrate higher efficacy in unresponsive CPP are key unmet needs**
- Improved understanding of disease pathology can guide investigations and support clinicians in selecting the best treatment for a patient, e.g. diagnosis and treatment of vascular congestion with ergot alkaloids reduces pain in ~80% of affected patients
- Although NSAIDs and opioids sufficiently manage pain, long-term administration carries risks of medication overuse headache and addiction; alternative therapies such as antidepressants are supported by weak clinical data and disease specific treatments such as hormones for endometriosis produce side effects in most patients

Current treatment paradigm

- Common chronic pain treatments are used and the paradigm depends on the physician's clinical experience and observation
- CPP with diagnosed aetiology, such as endometriosis or vascular congestion, receive specific treatments if they are available
- Paracetamol and NSAIDs are used 1st line
- They are considered efficacious, although individual patient response is variable
- Opioids are helpful in unresponsive CPP and they are prescribed similarly to other chronic pain syndromes, with caution due to concerns about abuse and addiction
- Tricyclic antidepressants may be used to avoid long-term use of opioids
- Counselling and relaxation therapy are also useful

CPP market opportunity and pipeline

Prevalence of CPP* (2015)
Millions of patients



- CPP is a common condition and it is known to affect between 3.8% of females in the UK and 14% or higher in the U.S.; however, data is not available for all geographies
- The total population of women affected, based on an extrapolation from U.S. and UK data, in Mundi / Purdue territories is ~82m patients
- The number of patients that seek treatment for chronic pain is ~26m, with the rest self-medicating, based on incidence data sourced from primary care visit records in the UK
- The pipeline for CPP drugs consists of treatments that target known underlying pathology of some CPP patients (e.g., the endometriosis pipeline consists of 27 products, with five in PhIII)

Note: *Average between U.S. and U.K. prevalence is applied to all geographies, ** Includes Malaysia, China, Singapore, Philippines, South Korea.
Source: Royal College of Obstetricians & Gynaecologists; American congress of obstetricians and gynecologists; Nuffields Obs&Gyn; Agency for Healthcare Research and Quality; Journal of the Society of Laparoendoscopic surgeons; Pharmaprojects; clinicaltrials.gov

DRAFT

Pain relief in stable angina is adequate, and the key unmet need is primary and secondary prevention of CVD, offering low opportunity to Mundi

Disease aetiology / pathophysiology

- The pathophysiology is well-established
- Deposition of atherosclerotic plaques on arteries that supply the heart muscle cause narrowing of the lumen of the artery, limiting blood supply at times of exertion, when demand is high
- Increasing or maintaining the patency of these arteries alleviates and prevents pain

Key unmet needs

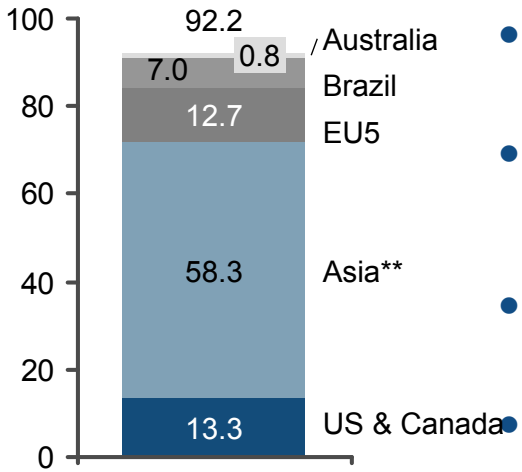
- Overall **symptom control in stable angina is adequate**; however, preventative agents are less able to control and reduce risk of myocardial ischaemia
- There is high unmet need in the **primary and secondary prevention of stable angina**, in order to maintain levels of physical activity, delay cardiac failure and reduce the risk of other cardiovascular events
- Nitrates are considered effective in relieving acute chest pain symptoms following exertion; however, they are not able to prevent the onset of pain on exertion in all patients and they are mostly used for symptom control only

Current treatment paradigm

- The current treatment paradigm consists of medications that prevent the onset of angina, reduce morbidity and offer pain relief
- Patients who suffer from stable angina are prescribed nitroglycerin (NTG), which increases the threshold of exertion at which pain ensues and thereby relieves pain
- If NTG is ineffective in relieving acute pain, patients are advised to attend an emergency department as this suggests a more serious diagnosis of myocardial infarction
- Preventative agents include beta-blockers, anti-platelet agents, statins, and ACE-Inhibitors
- NSAIDs are absent from the treatment paradigm and are contraindicated because of concerns about CVD

Stable angina market opportunity and pipeline

Prevalence of stable angina (2015)
Millions of patients



- The prevalence of stable angina is ~5% in those above the age of 20 years old in the U.S. and the U.K.
- There are ~90m angina patients in Mundi territories and is expected to rise due to higher rates of obesity globally
- The prescription is ~50% reflecting the variability in frequency of pain amongst patients, thus suggesting that the addressable population would be ~45m
- The pipeline for stable angina consists of 16 candidates, with only one aimed at the relief of acute pain, a nitrgoglycerin reformulation
- PhIII assets include a stem cell therapy agent by Baxter and a gene therapy agent by Taxus Cardium Pharmaceuticals

Note: *The rate varies significantly by country and ethnicity and is not reported for all geographies, thus the British Heart Foundation and CDC suggested values are used for this analysis
Source: British Heart Foundation; CDC; European Society of Cardiology; Nature Reviews Rheumatology

DRAFT

Although the patient population is small, chronic pain in SCD patients is frequent and concerns over NSAID/opioid side effects create a need for better tolerated analgesics

Disease aetiology / pathophysiology

- Sickle cell disease (SCD) is a chronic genetic blood disorder in which red blood cells become sticky and fragile, occluding blood vessels causing acute painful crises
- SCD patients also suffer from chronic pain which is though to be the result of a combination of bone tissue damage, spine compression, peripheral nerve infarction, central sensitization to pain and hyperalgesia

Key unmet needs

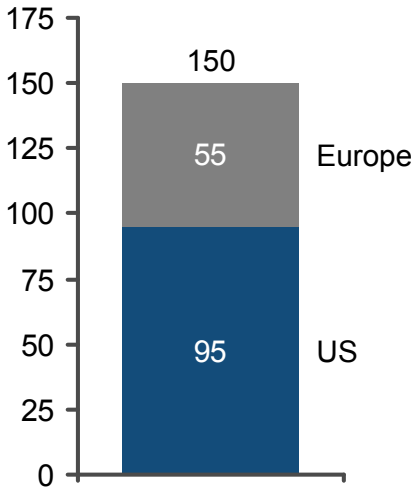
- Curative treatments and disease modifying agents that completely abolish acute crisis and chronic pain are a substantial unmet need in SCD
- **Therapies for management of chronic pain are also an unmet need in SCD, primarily due to tolerability and side-effect concerns**
- Significant side-effects of long-term frequent use of opioids may cause addiction and / or depression leading to a significant impact on quality of life, whereas NSAIDs are associated with gastric side-effects

Current treatment paradigm

- Available treatments include curative allogenic transplantation, disease modifying hydroxyurea and regular blood transfusions, and analgesics for pain relief
- Paracetamol, NSAIDs and opioids are used both for chronic disease and acute crises
- Weak opioids may be used for chronic pain, whilst stronger formulations are commonly used in acute settings
- Dosing of opioid medications is individualised for each patient, based on effective dosing regimes established from previous crisis
- Disease modifying agents also reduce the levels of pain experienced by patients

SCD market opportunity and pipeline

Prevalence of SCD* (2015)
Thousands of patients



- Sickle cell is a relatively common genetic disease, which mainly affects patients of Afrocaribbean or Mediterranean origin
- Prevalence varies by country due to the genetic makeup of the population and is highest in the U.S., southern Europe, sub-Saharan Africa and the Middle-East
- ~150,000 patients suffer from SCD in the U.S. and Europe, with ~20% experiencing daily pain
- The pipeline of disease modifying agents for SCD consists of 35 assets, however there are no assets in the pipeline targeting SCD-specific pain

Note: *Prevalence of SCD in Europe and the U.S. are shown because other geographies have low or unreported prevalence.
Source: CDC; Pharmaprojects; Journal of Pediatric Hematology/Oncology; clinicaltrials.gov

What is the ideal TPP for a visceral pain asset?

Considering the breadth of visceral pain, we outline some key attributes that should be demonstrated to achieve meaningful differentiation against current treatments in chronic pain conditions with recognised unmet needs

A TPP for the visceral pain asset	
Value proposition	• A targeted and/or disease-modifying therapy with improved efficacy and tolerability over currently-available treatment options
Indication and usage	• Indicated for specific visceral pain condition • Capability to address multiple symptoms of condition, which will complement the analgesic effect
Administration and dosing	• Oral administration or other form of administration causing minimum discomfort • Once daily or less frequent dosing
Efficacy	• Alleviates pain in more patients than current treatments, reducing pain severity and frequency • Prevents the re-occurrence of pain • Demonstrates consistent response across patients
Safety and tolerability	• Suitable for regular dosing without risk of medication overuse headaches and / or rebound headaches • No risk of abuse or dependence • Fewer side effects than opioids and / or NSAIDs
Pricing and reimbursement	• Pricing and reimbursement higher than OxyContin or celecoxib (prior patent expiry) supported by meaningful differentiation

Appendix

- Market overview
- Asset progress update
- Benchmarking research
- Indication prioritisation research
- MoA research

Note: we will continue to refine format for final presentation

We are already pursuing development of several promising novel MoAs with applicability in our indications of interest

	Differentiation / attractiveness	Stage (# assets)				Pain indications	Evidence
		PC	I	II	III		
Sigma-1 antagonists	• Differentiation: efficacy and side effects • Increased opioid analgesia without opioid-related side effects, thus potential use as opioid adjuvant therapy	7*		1		• NP • Nociceptive pain • Diabetic neuropathy • Cancer pain • POP	• Preclinical evidence supports a role in the treatment of pain with hyperalgesia and allodynia • Early stage human trials show good tolerability
TRKA inhibitors	• Differentiation: efficacy • Potential to offer strong, targeted efficacy in addressing pain	2**	3			• Arthritis pain • NP • Nociceptive pain • POP	• Animals models and early stage human trials show promising efficacy and tolerability
DHODH	• Differentiation: side effects • A novel approach to the treatment of autoimmune and inflammatory diseases • Single pipeline asset is also a positive allosteric modulator of the GABAA receptor, does not cross the BBB, is non-sedative, with no abuse potential		1			• NP	• A significant reduction of pain in all investigated models that is long-lasting and without adverse CNS side effects
TRPV1 antagonists	• Differentiation: side effects • Not involved in body temperature regulation or heat perception and may avoid associated side effects	1	3	1		• Arthritis pain • NP • Nociceptive pain • Post-herpetic neuralgia	• Shown to be well tolerated in early stage human trials
CGRP antagonists	• Differentiation: efficacy • Efficacious and quick in reducing migraines, long duration of action • Potential for better dosing and easier administration	4		2	1	• Migraine	• Positive Phase II data showing that CGRP therapy is highly effective in reducing the number of migraines

Note: *Two in combine VG sodium channel inhibition. **One in combines with MAPK inhibition.

Note: we will continue to refine format for final presentation

In addition to our MoAs in development, several additional MoAs were identified as attractive based on differentiation, applicability and clinical evidence

		Differentiation / attractiveness	Stage (# assets)			Pain indications	Evidence
			PC	I	II		
Opioids	Biased opioid agonists	• Differentiation: side effects • No side-effects of traditional opioids and non-addictive	2			• NP • Migraine	• Preclinical studies suggest efficacy and lack of addiction liability
Ion channels	$Na_v1.7$ inhibitors	• Differentiation: side effects • Could be efficacious while avoiding side effects of non-specific Na_vs inhibitors	7	2		• NP • Nociceptive pain • POP	• Preclinical studies establish role in pain signaling • $Na_v1.7$ causally linked to human pain disorders • Human trials show good tolerability
	$Na_v1.8$ inhibitors	We currently have a Nav1.7 discovery program with Anabios	1		1	• Arthritis pain • NP • POP	
	$Na_v1.7/1.8$ inhibitors	• Differentiation: side effects • Could provide synergistic efficacy while avoiding side effects		1		• NP	• Preclinical studies demonstrate antiallodynic effect of dual inhibition
	TRPA1 antagonists	• Differentiation: side effects • Not involved in body temp regulation and may avoid associated side effects		1		• NP • Diabetic neuropathy • POP	• Analgesic efficacy is well established in preclinical models of pain
Neurotransmitter modulators	$GABA_A$ $\alpha2/\alpha3$ PAM*	• Differentiation: side effects • Can have dual effects on emotions and pain, while avoiding sedative side effects	1	1		• Unspecified pain	• Analgesic effect is well established in a PC model of neuropathic and inflammatory pain
	NMDA-NR2B antagonists	• Differentiation: side effects • Could have fewer side effects than non-specific NMDA antagonists	4		1	• NP	• Efficacy in chronic pain and depression in PC models and early stage human studies
	mGluR5 NAM*	• Differentiation: efficacy • Potential for use as adjunctive therapy to SSRIs / SNRIs with good safety	3		2	• Chronic pain (unspecified) • Migraine	• Positive data from PhII trials and animal models of several CNS diseases

Highly attractive

Note: * PAM: positive allosteric modulator; NAM: negative allosteric modulator.

DRAFT

We will not currently pursue cannabinoid receptor agonists, due to a lack of scientific evidence for efficacy in pain and the potential for severe side effects

CB1 agonism has limited pain efficacy and severe side effects

- CB1 is a major target of current cannabinoid agonists, either alone or in combination with other cannabinoid receptors
- Non-selective CB1 agonism has demonstrated limited efficacy in pain and side-effects, including depression and suicide, whilst supporting studies have been of moderate quality
  - there is some evidence for efficacy in neuromotor conditions, such as MS-related spasticity and epilepsy (e.g. GW Pharma's products Sativex and Epidiolex)
- Selective CB1 agonists are also associated with psychiatric side-effects, including depression and psychosis, which led to the withdrawal of a Sanofi product, rimonabant, from the European market in 2009

Specific CB2 agonists may avoid side effects, but with limited efficacy data

- Some research is now focusing on CB2-specific agonists, which could have anti-nociceptive and anti-inflammatory properties without the side effects associated with CB1 agonism
- CB2-specific agonists were trialed for the treatment of osteoarthritis and dental pain, with results of a trial from GSK for the latter indication failing to demonstrate clinically meaningful analgesia against placebo in a PhII randomized control study

FAAH inhibitors have limited efficacy and safety concerns

- FAAH inhibition has demonstrated evidence of preclinical efficacy and could potentially avoid the psychiatric side effects of cannabinoid receptor agonism
- However, clinical trials by Pfizer that targeted osteoarthritis of the knee failed to demonstrate clinically significant analgesia
- There is also the potential for serious safety concerns, following the death of a patient in a PhI trial of an FAAH inhibitor conducted by Bial

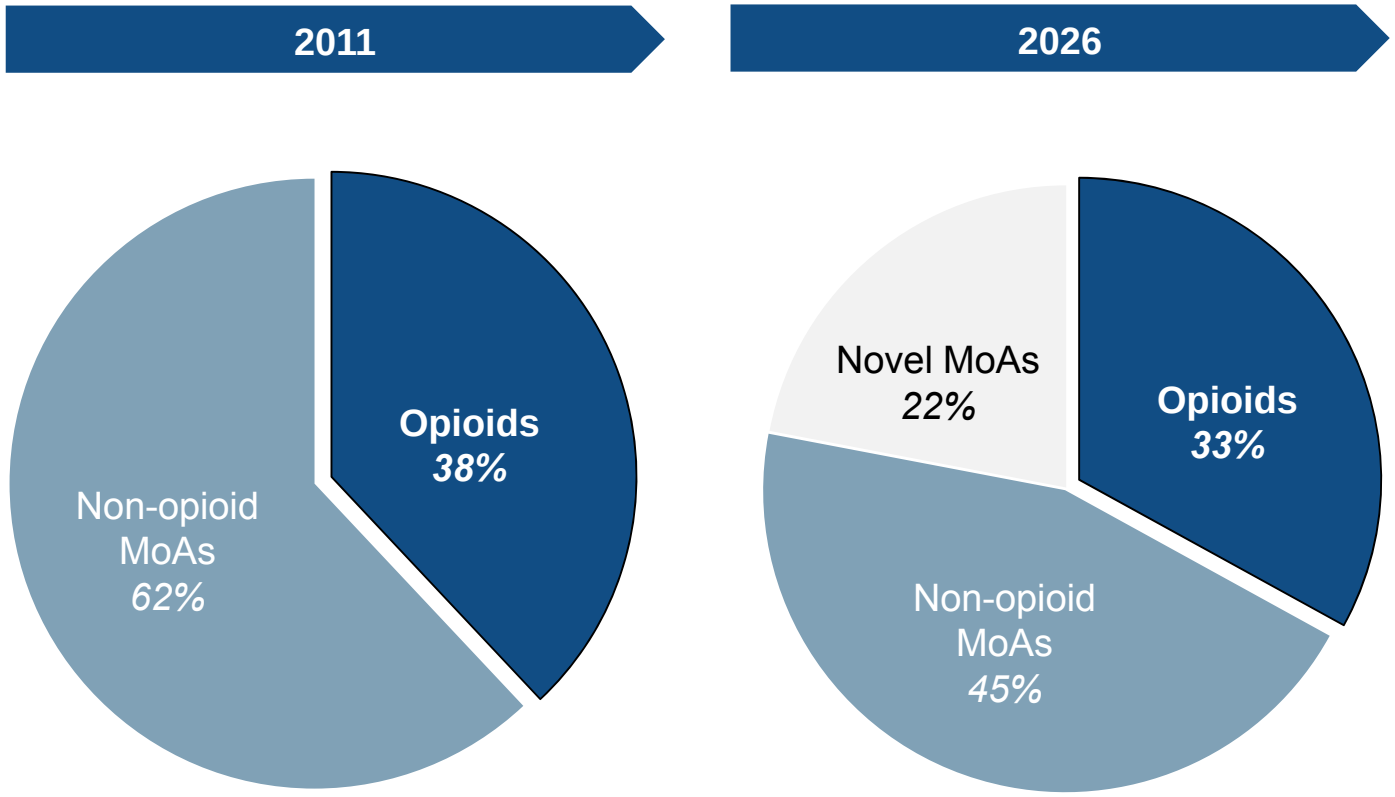
Source: PharmaProjects; RnD Insights

DRAFT

While opioids will remain a key MoA in the future, the market is expected to adopt novel MoAs and reduce use of opioids and other established MoAs

Expected evolution of global pain market sales by MoA

INDICATIVE



Novel MoAs:
- Subtype selective ion channel mobulators
- NGF modulators
- Kinase modulators (p38/MAPK, TrkA)
- Others

Non-opioid MoAs:
- COX2 inhibitors
- TRPV1 agonists
- Neurotropin
- Local anaesthetics
- Simple analgesics
- Anti-depressants
- Anti-epileptics
- Anti-migraine

Source: Decision Resources

DRAFT

The global pain regulatory landscape remains complex, which will impact our clinical development strategy and may affect opioid use

Global guidelines will have a significant impact on clinical development strategies for pain medications

- Divergence between new US and EU guidelines on pain indication registration requirements may impact global development programmes
- Global clinical trials will need to be clearly planned and defined in order to:
  - achieve approvals for the same indications across geographies
  - not incur significant increases in trial time and costs
  - maintain consistent labelling and claims

- Guidelines in Japan and China may be converging on global requirements, potentially enabling us to include patients from these geographies in global trials
- Potential removal of need for standalone trials in China and Japan may require their input into PhIII trial design to ensure potential for regulatory approval

New prescribing guidelines will impact opioid sales in the US whilst opioid access is still restricted in emerging markets

- New CDC and FDA guidelines released this year aim to limit opioid usage and are therefore likely to dampen opioid sales in the US

- The estimated impact on OxyContin peak sales is ~$20-47M
- Medicare and Medicaid plans are at more risk than commercial plans, as the latter are not required to follow new guidelines

Longitudinal Patient Analysis and stakeholder research will help determine the impact of these guidelines

- Across APAC, access to opioids is still heavily restricted, meaning these geographies still underuse opioids and undertreat pain

Note: * The public consultation on this guideline ended in late March 2016
Source: FierceBiotech; Purdue management

DRAFT

Big pharmas are moving to pursue pain only opportunistically, creating an opening for us to take the lead in the broader pain market

NOT EXHAUSTIVE

Examples of **large pharma divesting out of pain** and concentrating on areas of higher return

Examples of **smaller companies further expanding** strategically in pain

Company	Asset(s)/Action	Key market activity
Johnson & Johnson	Divest fulranumab, anti-NGF	Janssen returned rights to Amgen due to 'strategic portfolio prioritisation'. Amgen considering options
Pfizer	Divest pain portfolio	Pfizer is divesting pain portfolio and closing pain R&D site in Cambridge, UK, but is funding ongoing trials (e.g. tanezumab)
Boehringer Ingelheim	Divest pain portfolio	BI sold rights to entire pain portfolio to Centrexion Therapeutics to focus on neuropsychiatric conditions
GRÜNENTHAL	Expansion in new markets	Purchased Almirall's Mexican operations, including rights to pain assets, and received rights to AcelRx's PCA drug, Zalviso, for Europe and Australia
CENTREXION THERAPEUTICS	Acquire pain portfolio	Purchase of BI's pain portfolio to build a company of 'non-opioid, non addictive pain treatments'

The complex, high risk and poorly understood nature of pain make it challenging for those who do not know it as well as us

Note: *Based on anectdotal recent evidence, in depth analysis of competitive strategy not examined
Source: FiercePharma; FierceBiotech

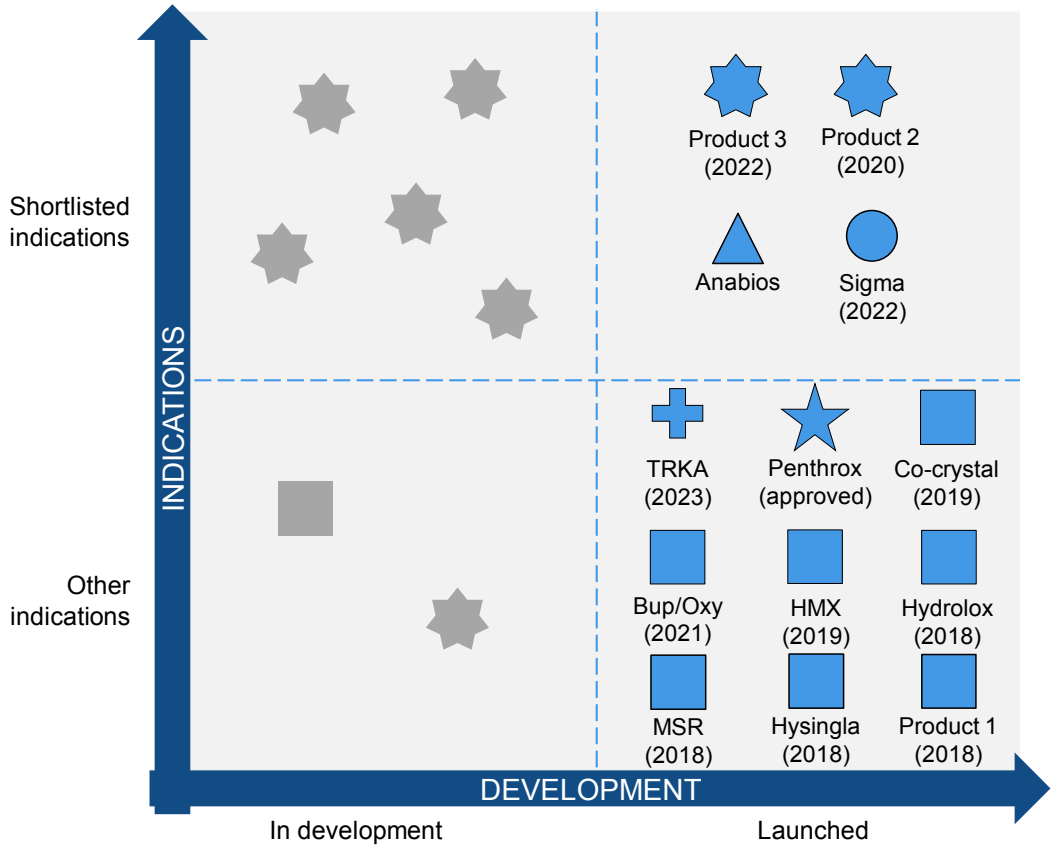
DRAFT

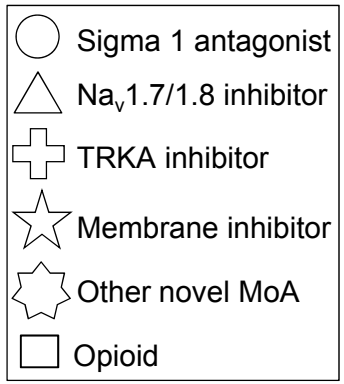
Our 2026 vision: progressive portfolio development to achieve our strategic goals

2026

INDICATIVE

A globally oriented pipeline, designed to protect our base while innovating for future expansion





With a range of novel MoAs addressing key unmet needs in attractive pain indications, such as NP, cancer pain, and migraine, our pipeline can support us on our way to becoming a leader in pain

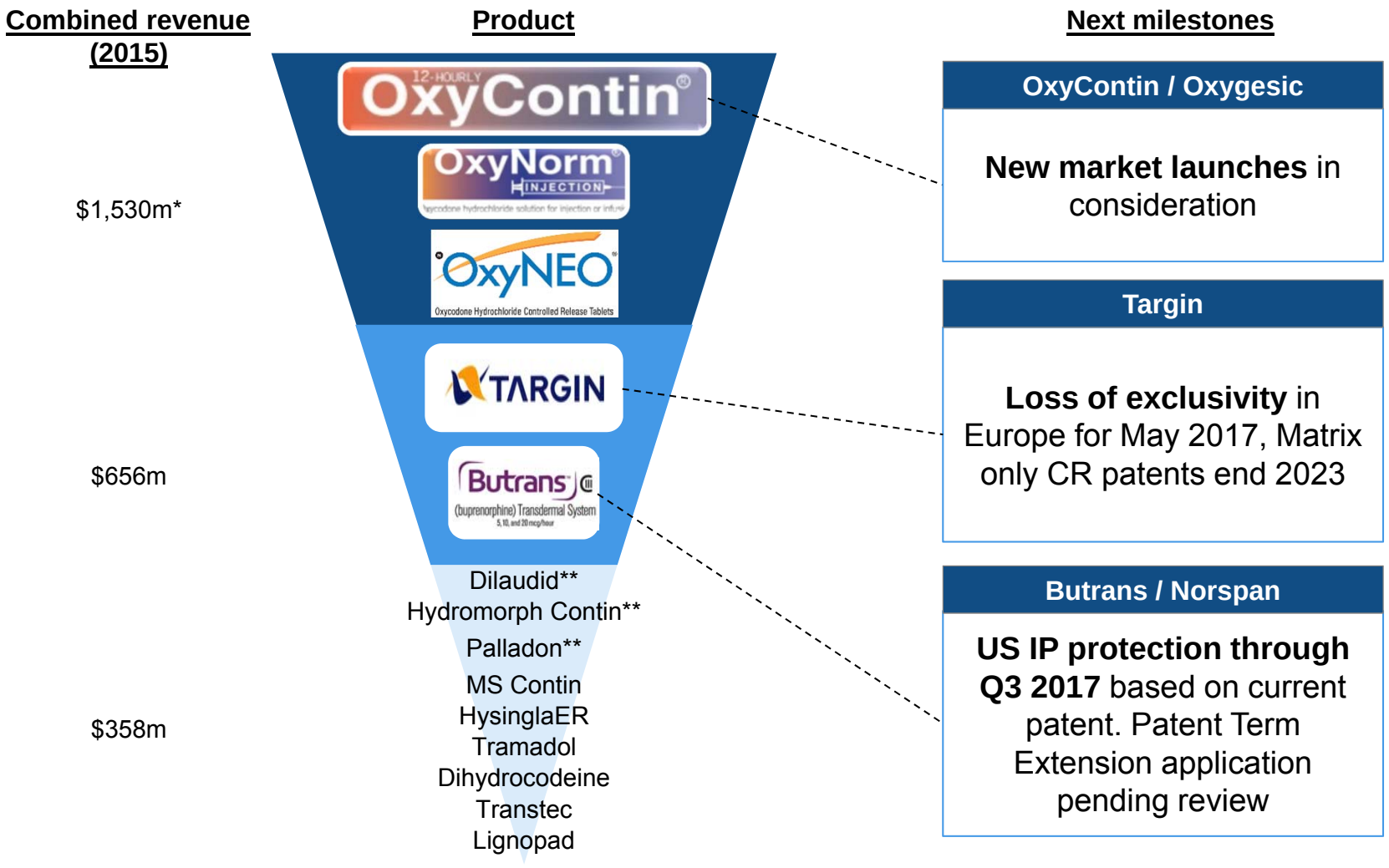
DRAFT

We can use our strong positioning in pain and opioids to take advantage of opportunities arising in the market to expand beyond our core

Key opportunities	MDP/Purdue Strength alignment
• Significant unmet needs across pain conditions	• Established pain portfolio and pain marketing capabilities
• Scientific advances leading to potential novel MoAs and treatment options	• Established knowledge and experience of pain clinical development programmes
• Expanding access to drugs in emerging markets	• Established pain portfolio and global presence
• Increasing global pain patient numbers due to health factors such as obesity and aging	• Established pain portfolio with global presence and global marketing capabilities
• Big pharma exiting pain (Pfizer, BI) creating a leadership gap in pain	• Established market leadership and credibility • KOL relationships and reputation in pain

DRAFT

The Mundi/Purdue portfolio is concentrated on strong opioids and have out-performed industry norms for lifetime brand performance. This will not continue



Note: * Total OxyContin and other Oxycodone sales; ** Total Hydromorphone sales

Note: we will continue to refine format for final presentation

We have identified a number of attractive pain indications and MoAs to pursue

This will allow us to truly innovate in pain

	Prioritised	***Rationale***
Indications	**Neuropathic pain**	High unmet need for an effective treatment and branded price potential if products are differentiated
	Fibromyalgia	Very high unmet need for effective treatments with possibility for advancing science to identify new targets
	Migraine	Unmet need for effective prophylaxis for chronic patients with branded price potential
	Cancer pain	Significant need for a strong, non-opioid analgesic with reduced side effects
	Orphan / niche pain indications	Potential to address the high unmet needs specific to these niche indications
MoAs	**Sigma-1 antagonist** *(ongoing)*	Consistency & promise of Esteve programme in neuropathic pain
	Novel / biased opioids *(ongoing)*; **TRKA inhibitors** *(ongoing)*	Potential in chronic pain for improved efficacy / safety trade-off
	TRPA / TRPV antagonists *(ongoing)*; **Nav1.7 / Nav1.8 inhibitors** *(ongoing)*	Potential across a wide range of neuropathic and nociceptive pain indications with fewer associated side effects
	GABA2/3 modulators; **NMDA-N2RB antagonists**; **DHODH inhibitors** *(ongoing)*	Potential in neuropathic pain with fewer CNS-associated side effects
	mGluR5 modulators; **CGRP antagonists** *(ongoing)*	Potential in migraine with high efficacy, dosing and administration

Source: Management

Note: we will continue to refine format for final presentation

In addition to these indications, we are evaluating a number of orphan / niche indications for their potential attractiveness

	Description	Unmet needs
Phantom limb pain	• Pain (typically chronic) experienced by limb amputees in the limb that has been amputated	• Mechanism not understood; no standard treatment regimen
Post-herpetic neuralgia refractory to treatment	• Pain experienced ≥3 months after a herpes zoster occurrence that is refractory to treatment	• Many patients do not respond to conventional treatment
Complex regional pain syndrome	• A chronic pain syndrome that largely develops in extremities after some form of acute trauma	• Few or no approved therapies specifically for CRPS; oral opioids have poor efficacy
HIV-related peripheral neuropathy	• Neuropathic pain related to an underlying HIV diagnosis, both disease and drug-induced	• Poorly diagnosed and considered lower priority compared to general management of disease
Opioid refractory cancer pain	• Pain experienced by cancer patients that is refractory to opioid treatment	• Patients do not respond to opioid treatment and may have severe pain
CINP refractory to treatment	• Chemotherapy-induced neuropathic pain that is refractory to opioid treatment	• Diagnosis rates are low compared to other cancer pain and there is no way to prevent it
Intractable pain at end stage disease	• Chronic, severe, unrelenting pain experienced by patients with end stage disease	• Patients do not respond to conventional treatment, only potent opioids may control pain
Persistent idiopathic facial pain	• Pain along the trigeminal nerve that cannot be attributed to other cranial neuralgias	• Difficult to diagnose and more difficult to treat than other facial pain syndromes
Pain in chronic kidney and/or liver impairment patients	• Pain experienced by CKD* patients or ones with liver conditions, e.g. hepatitis, NAFLD*	• Treatment has to be compatible with the underlying condition, while treating the pain well
Pain in the very elderly (>75 years)	• Pain experienced by elderly patients that may be related to a variety of underlying conditions	• Pain may be difficult to assess and treat, e.g. due to communication or physical limitations
Multiple sclerosis-associated pain	• Pain that may be experienced by patients with Multiple Sclerosis	• Complex pain, making it difficult to treat and lower priority compared to other symptoms
Pain in CYP2D6-deficient patients	• Pain felt by patients with mutations in the CYP2D6 gene (a drug metabolising enzyme)	• Patients at risk of poor responses to or adverse events from opiates (e.g. codeine, tramadol)

Note: *CKD: Chronic kidney disease; NAFLD: Non-alcoholic fatty liver disease.
Source: EMA; FDA; Management; Medscape; MS Society

DRAFT

Market Entry Drivers

- Formulation success + 1-yr stability
- Length/complexity of the Phase 3 program
  - For approval
  - For commercial differentiation
  - Shorter-term trials (eg bunionectomy) for acute pain
  - Longer-term trials (eg low-back-pain) for chronic pain
- FDA Fast Track, Accelerated, Breakthrough, Priority Review

Christian Darland

To include? Or to back up?

DRAFT

DRAFT